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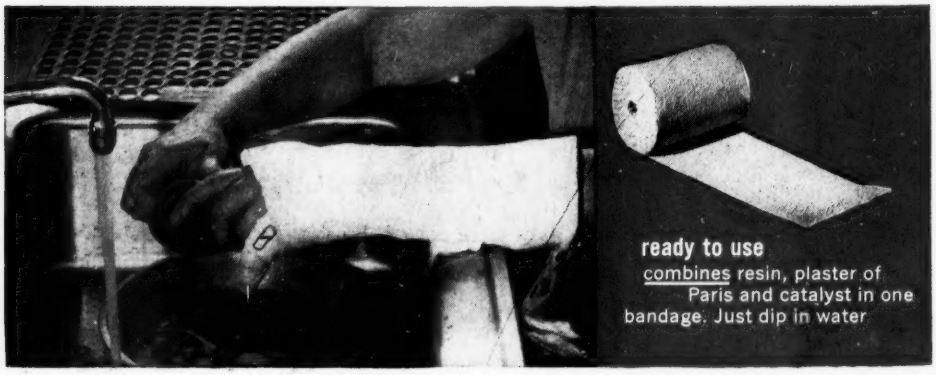

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CONTENTS

The Scope of Radical Surgery in the Treatment of Malignant Tumors of the Extrahepatic Biliary Tract. *Frank Glenn, M.D., F.A.C.S., New York, New York, and Daniel M. Hays, M.D., Los Angeles, California* 529

Studies of Blood Volume and Transfusion Therapy in the Korean Battle Casualty. *Theodore C. Prentice, M.D., Captain, M.C., John M. Olney, Jr., M.D., 1st Lt., M.C., Curtis P. Artz, M.D., F.A.C.S., Major, M.C., and John M. Howard, M.D., Captain, M.C., Washington, District of Columbia* 542

Prognosis in Cancer of the Uterine Cervix Based on the Vaginal Smear Before Treatment; SR—The Sensitization Response. *John B. Graham, M.D., F.A.C.S., Ruth M. Graham, B.S., and Winifred Liu, M.D., Boston, Massachusetts* 555

A Clinical Study of Two Hundred One Cases of Regional (Segmental) Colitis. *Harold W. Neuman, M.D., C.M., J. Arnold Bargen, M.D., and Edward S. Judd, Jr., M.D., F.A.C.S., Rochester, Minnesota* 563

The Pathology of Regional (Segmental) Colitis. *Harold W. Neuman, M.D., C.M., and Malcolm B. Dockerty, M.D., Rochester, Minnesota* 572

Experimental Study of Pulmonary Histopathology Following Positive and Negative Pressure Respirations. *Robert C. Waltz, M.D., Charles A. Hubay, M.D., F.A.C.S., Jay L. Ankeney, M.D., and Jane Merrill, M.D., Cleveland, Ohio* 580

Valvulotomy for the Surgical Relief of Aortic Stenosis. *William H. Muller, Jr., M.D., F.A.C.S., and Maurice Hyman, M.D., Los Angeles, California* 587

Studies of the Response of the Autonomic Nervous System Following Combat Injury. *Robert R. Stahl, M.D., Captain, M.C., U.S.A.F., Curtis P. Artz, M.D., F.A.C.S., Major, M.C., U.S.A., John M. Howard, M.D., Captain, M.C., U.S.A.R., Houston, Texas, and Fiorindo A. Simeone, M.D., F.A.C.S., Cleveland, Ohio* 595

CONTENTS CONTINUED ON PAGE 7

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CONTENTS FOR NOVEMBER, 1954 — CONTINUED

The Marginal Anastomoses of the Arteries to the Large Intestine. *J. V. Basmajian, M.D., Toronto, Canada* 614

Endocrine Interrelations Concerned with the Postoperative Renal Response to a Water Load. *Richard N. deNiord, Jr., M.D., and Mark A. Hayes, M.D., Ph.D., F.A.C.S., New Haven, Connecticut* 617

Diverticulitis and Carcinoma of the Colon; Differential Diagnosis. *Bentley P. Colcock, M.D., F.A.C.S., and Robert E. Sass, M.D., Boston, Massachusetts* 627

Reconstruction of Posterior Portion of Urethra. *Henry M. Weyrauch, M.D., F.A.C.S., and Ranulf P. Beames, M.D., San Francisco, California* 634

EDITORIAL

The Problem of the Fractured Hip. *Paul C. Colonna, M.D., F.A.C.S., Philadelphia, Pennsylvania* 638

THE SURGEON AT WORK

A Simplified, Inexpensive Technique in Hysterosalpingography. *Arthur J. Bendick, M.D., New York, New York* 642

The Technique of Subtotal Gastrectomy for Duodenal Ulcer (Radical Distal Partial Gastrectomy). *Richard H. Sweet, M.D., F.A.C.S., Boston, Massachusetts* 647

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

Thoracic Surgery. By Richard H. Sweet. 2nd ed. 653

The Thyroid; a Physiological, Pathological, Clinical, and Surgical Study. By T. Levitt 653

Ulcerative Colitis; and Its Surgical Treatment. By Bryan N. Brooke 654

Applied Cytology. By G. R. Osborn 654

A Manual on Cardiac Resuscitation. By Robert M. Hosler 654

Anatomy for Surgeons; the Head and Neck. By W. Henry Hollinshead. Vol. 1 655

Medical History of the Second World War; Surgery. Edited by Sir Zachary Cope 655

Books Received 656

INTERNATIONAL ABSTRACTS OF SURGERY

Contents ..... i–viii

Collective Review: Breast Cancer and Pregnancy or Lactation. *Edward F. Lewison, M.D., F.A.C.S., Baltimore, Maryland* 417–424

Abstracts of Important Contributions in the Current Surgical Literature 425–520

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SURGERY
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VOLUME 99 NOVEMBER, 1954 NUMBER 5

THE SCOPE OF RADICAL SURGERY IN THE TREATMENT OF MALIGNANT TUMORS OF THE EXTRAHEPATIC BILIARY TRACT

FRANK GLENN, M.D., F.A.C.S., New York, New York, and
DANIEL M. HAYS, M.D., Los Angeles, California

THE malignant tumors of the extrahepatic biliary tract, that is, the gallbladder, extrahepatic ducts, and ampulla of Vater, have long justified a reputation for extreme resistance to therapy. During the past 10 years many surgeons have hoped that the application of the concept of more radical and extensive resection to this tumor group might alter this prognosis.

In The New York Hospital—Cornell Medical Center, as in similar medical institutions, the handling of cases of carcinoma of the gallbladder by extensive hepatic excision and the en bloc resection of other surrounding structures was planned (Fig. 2) and, in many cases, executed. Radical pancreatoduodenectomy was advocated as a curative operation in cases of ductal and ampullary carcinoma, with extension of resection to include other structures, such as the portal vein, if necessary, to circumscribe the margins of gross tumor.

The present report deals with the care of patients with these tumors during a 21 year period from September 1, 1932 to September 1, 1953; in the latter half of which the concept of radical resection was paramount in this clinic. Almost all of the ealier patient-candidates for these procedures are now dead. It is thus possible to evaluate the effect on cure and longevity in such cases with accuracy.

The inclusion of ampullary carcinomas in this triad is logical, for morphologically and in respect to natural development they closely resemble the ductal carcinomas.[1]

PRESENTATION OF DATA FROM THE NEW YORK HOSPITAL—CORNELL MEDICAL CENTER SERIES[2]

Carcinoma of the gallbladder. Carcinoma of the gallbladder was established by operation and biopsy or by autopsy in 68 cases. Four cases were excluded in which carcinoma was apparently metastatic from tumors of the liver or pancreas.[3] The male to female ratio was 1 to 2.8 (Table II). The age range was from 37 to 83 years with the majority of patients over 60 years of age. The average age was 62.5 years and the distribution was as follows: 2 patients were in the age group from 35 to 44 years, 6 from 45 to 54, 31 from 55 to 64 years, 25 from 65 to 74, and 4 were in the group from 75 to 84 years old.

An analysis of all cases of patients 65 years of age or older with biliary tract disease seen in

From the Department of Surgery, The New York Hospital—Cornell Medical Center, New York.

[1]Willis believes that many incompletely studied "ampullary" and "pancreatic-head" carcinomas actually originate in the choledochus.

[2]Pavilion (ward) patients.

[3]Also excluded are numerous cases of upper abdominal carcinomatosis in which the primary site was in doubt at either operation or autopsy.

TABLE I.—CARCINOMA OF THE EXTRAHEPATIC BILIARY TRACT

	Operative demonstration (biopsy)	Autopsy finding (c or s operation and biopsy)	Total
Carcinoma of the gallbladder	51	17	68
Carcinoma of the ductal system Cystic duct (3) Common hepatic duct (6) Choledochus (6)	5	10	15
Carcinoma of the ampulla of Vater	10	10	20
			103

this medical center during the period of study (362) reveals that in almost 10 per cent of those explored carcinoma of the gallbladder or biliary ducts was found. There were 328 operative cases of nonmalignant disease (acute and chronic cholecystitis and choledocholithiasis) and 34 of carcinoma of the gallbladder or extrahepatic ducts (ampullary carcinomas excluded).

Thirty-eight (56 per cent) of the patients with gallbladder neoplasms had noted symptoms referable to the biliary tract for 1 year or more. Eighteen (26 per cent) had endured such complaints for 10 years or more, and 15 (22 per cent) for a period of 20 to 30 years. In at least 10 patients an x-ray diagnosis of chronic cholecystitis or cholelithiasis was established at least 1 year prior to admission for surgery; in 6 patients, at least 5 years prior to this admission; and in 4 patients an x-ray diagnosis of gallbladder disease had been established for at least 10 years prior to operative intervention for carcinoma of the gallbladder.

TABLE II.—THE INFLUENCE OF SEX, AGE, AND A HISTORY OF BENIGN BILIARY TRACT DISEASE IN CASES OF CARCINOMA OF THE EXTRAHEPATIC BILIARY TRACT

	Carcinoma of the gallbladder	Carcinoma of the extrahepatic ducts	Carcinoma of the ampulla of Vater	Total
Total No. of patients studied	68	15	20	103
Sex Male	18	9	15	
Female	50	6	5	
Age, years Under 50	4	2	5	
50–64	35	8	9	
65 and over	29	5	6	
Average age	62.5	62.5	57.6	
Average duration of biliary tract symptoms, years	5.3	2.6	Less than 1 yr. (5 cases)	
X-ray findings of cholecystitis (for at least 2 years prior to operation)[1]	10(15 per cent)	1	0	

[1]Autopsy in 9 cases.

The detailed symptomatology is given in Table III. We found it convenient to group cases of carcinoma of the gallbladder according to the type of benign biliary tract disease which they simulate (Table IV). In over 70 per cent of these cases of carcinoma of the gallbladder, the symptoms would be identified by any physician as those of benign biliary tract disease. Ninety-five per cent of the preoperative cholecystograms (44) demonstrated nonfunction of the gallbladder or calculi.

Cytologic study of the duodenal aspirate in 3 of these cases revealed cells which were designated as class I or II (Papanicolaou).[1] Similar studies on bile removed from the biliary tract at operation and from peritoneal fluid (in disseminated cases) revealed cells which were uniformly designated as classes III to V.

The planned procedure in recognized cases of nondisseminated carcinoma of the gallbladder in this center includes a resection of all of the liver tissue which comprises the gallbladder bed (Fig. 2). The portal vein, hepatic artery, and hepatic duct are identified and skeletonized with resection of the peritoneum and retroperitoneal tissue anterior to and between these structures and the gallbladder bed. This dissection is then carried inferiorly to the duodenum, with transection of the cystic duct as it enters the choledochus. Included in the operative specimen is the peritoneum and lymphatic tissue anterior to the choledochus extending as far to the left as the pylorus. If the omentum is adherent to the gallbladder or liver in this region, it is included in the resection.

The operative treatment of these 59 patients with carcinoma of the gallbladder may be separated into the 40 cases in which the nature

[1]Papanicolaou classification: class I or II—no evidence of malignancy; class III or IV—increasingly suggestive of malignancy; and class V—conclusively malignant.

of the lesion was recognized and in which no curative procedure was deemed feasible, and the 19 cases in which a potentially curative operation was performed (Table V). The latter group includes 9 patients in whom the lesion was correctly identified by biopsy (frozen section), 6 cases in which it was suspected but not confirmed by biopsy,[1] and 4 cases in which the surgeon did not suspect the presence of a cancer. The 15 patients in the first two categories were treated by cholecystectomy together with the removal of liver and other surrounding structures.[2] One of the 4 patients in the third group was subjected to a secondary excision of the gallbladder bed.[3] In the remaining 3, the lesion was believed to be localized[4] and re-exploration was deemed unnecessary.

All patients included in the group subjected to palliative procedures (40) are deceased (Table VI). Among the 19 patients in whom potentially curative procedures were carried out there are 4 survivors without evidence of recurrence at the time of publication. One of these patients has survived for 1 year, 2 for 4½ years, and the fourth for 7½ years following surgery. The tissue sections from these patients have been reviewed and the presence of carcinoma of the gallbladder reconfirmed.

The 10 patients who survived for 1 year or more following surgery (Table VI) were subjected to special study. It is of interest that in 3 (30 per cent) of these patients, including the longest survivor, the carcinoma was not recognized as a neoplasm by the operating surgeon. When recognized (7 cases) the tumor was usually described as a localized thickening of the gallbladder wall; and if the organ was opened, as a papilliform friable mass in the lumen of the gallbladder. The 3 cases not recognized as carcinoma of the gallbladder in this group included: (a) 1 case of acute cholecystitis, (b) 1 in which cholecystectomy was preceded by a cholecystostomy and the tumor identified incorrectly as an inflammatory tract, and (c) 1 case of simple chronic

[1]Two frozen section reports were misleading in this regard. In all of these cases the diagnosis was later established at autopsy.
[2]In 1 case sufficient to constitute a radical pancreatoduodenectomy. The survival period for this patient was 10 months. Simple cholecystectomy was performed in 1 case.
[3]The survival period in this patient was 1 year.
[4]One was described as carcinoma in situ.

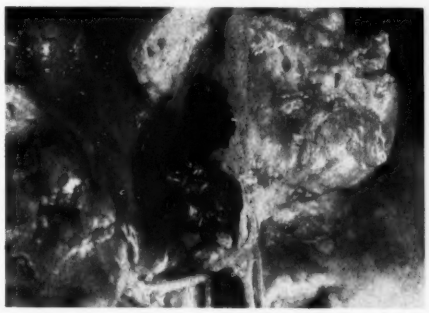

Fig. 1. Carcinoma of the gallbladder associated with longstanding cholecystitis and cholelithiasis with extensive metastases demonstrated at portmortem examination. The operative findings in 68 per cent (40 cases) of the explorations performed for this condition in the present series were similar; that is, neoplasms already beyond control by radical excision.

cholecystitis in which the failure to recognize the lesion can only be attributed to its minute size.

Carcinoma of the extrahepatic biliary ducts. The presence of carcinoma of the extrahepatic biliary ducts was established by operation and biopsy in 5 cases, by operation followed by autopsy in 8 cases, and by necropsy alone in 2 cases. The female to male preponderance, so striking in patients with carcinoma of the gallbladder, was not apparent in this group (Table II). The average age of these individuals, however, was also 62.5 years. Six patients had longstanding biliary tract symp-

TABLE III.—THE SYMPTOMATOLOGY IN CARCINOMA OF THE EXTRAHEPATIC BILIARY TRACT

Symptoms	Carcinoma of the gallbladder		Carcinoma of the extrahepatic ducts		Carcinoma of the ampulla of Vater	
	No.	Per cent	No.	Per cent	No.	Per cent
Abdominal pain	50	74	5	33	11	55
Radiation to back	7		1			
Jaundice	30	44	14	93	18	90
Weight loss	43	63	7	47	12	60
Nausea and vomiting	16	24	3	20	8	40
Chills, fever	7	10	2	13	3	15
Palpable mass (noted by patient)	3	4	0		0	
Melena (gross)	0		2	13	3	15
(occult)	18	26	10	66	14	70
Total No. of cases	68		15		20	

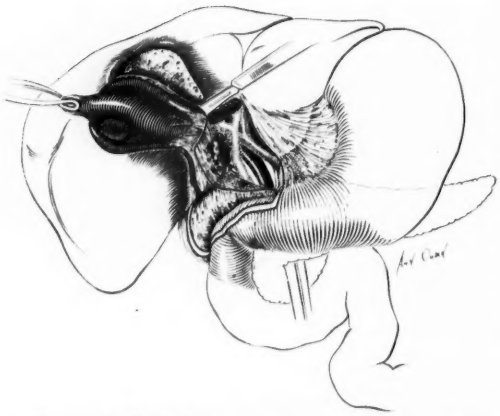

Fig. 2. Radical cholecystectomy for carcinoma of the gallbladder, including resection of the gallbladder bed, the peritoneum, and retroperitoneal tissues of the gastrohepatic and pericholedochal areas. Unfortunately, because of frequent early hepatic metastasis and the difficulty in identifying small carcinomas, the procedure illustrated here is only feasible in a small percentage (20 per cent in this series) of patients with gallbladder cancer.

toms (average 4.6 years in length); and 2 had known cholelithiasis.[1] The symptomatology is presented in detail in Table III. Jaundice was noted in 14 patients (93 per cent) of this group. Ten patients (66 per cent) had occult blood in preoperative stool specimens.

Cytologic study of the duodenal aspirate in 4 of these cases revealed cells designated as classes I to III (Papanicolaou). As in carcinoma of the gallbladder, however, the bile in ducts adjacent to the tumor, when removed at operation, uniformly contained cells designated class V. As a control of this method the study by cytologic techniques of the duodenal aspirate in 47 patients without cancer was employed. Forty-two of these were designated as classes I or II; 4 were class III; and 1 class V according to the classification of Seybolt, Papanicolaou, and Cooper.

Operative cholangiography was employed in 7 instances (5 patients); but in only 1 case was a definitive demonstration of a ductal carcinoma made. In this case a tumor was indicated by the failure of retrograde filling of the hepatic duct, produced by an almost complete obstruction by carcinoma (Fig. 3). A portal venogram was employed to demonstrate the absence of encroachment on the portal vein in 1 case. A significant distortion of the duodenum as seen by gastrointestinal x-ray series was noted in 5 patients, all with advanced lesions. In the remaining cases this study was not diagnostically helpful.

Only 2 patients with biliary duct carcinoma were deemed candidates for curative surgery, i.e., radical pancreatoduodenectomy; while in the remaining 11 operative patients diagnosis and palliation were the only aim in therapy.[2] The survival period in 12 of these patients was less than 6 months (Table VI). It is of interest that calculi were associated with carcinoma in almost half of the cases which were autopsied.

Carcinoma of the ampulla of Vater. A diagnosis of carcinoma of the ampulla of Vater was established by operation (and biopsy only) in 10 cases; and at autopsy, in confirmation of operative findings, in 10 additional cases. Three-quarters of these tumors occurred in males. The age range was from 38 to 80 years, with an average age of 57.6 years. Five of these patients (25 per cent) had biliary tract symptomatology for a period of at least 1 year. In the remaining 15 patients the duration of symptoms was several months. Ninety per cent of these patients were jaundiced; and 15 per cent displayed gross melena (Table III). In 14 (82 per cent) of the operative cases, the preoperative stool specimen was guaiac positive for blood.

Duodenal contents were studied preoperatively by cytologic techniques in 3 cases (5 studies), all of which were designated classes I or II (Papanicolaou). Operative cholangiography was employed four times (2 patients) in this group, and in 1 case beautifully demonstrated the ampullary tumor (Fig. 4). Portal venography was also employed in 1 instance to eliminate the possibility of extension into the wall of this vessel. In 1 patient with an ampullary lesion, the biliary tract was filled with air (by x-ray study) secondary to a choledochoduodenal fistula.

The gastrointestinal series in 4 instances revealed a distortion of the duodenum in the ampullary region, suggesting a tumor. All of

[1]For 8 years and 2 years respectively.

[2]Most of these cases were seen in the first decade of the study At least 4 patients would have been subjected to radical resection had they been seen at a later date.

Fig. 3. N.Y.H., Case No. 534 663. Carcinoma of the hepatic duct (arrow) demonstrated by a failure of retrograde filling during operative cholangiography. A lesion in this portion of the extrahepatic biliary tract was not suspected prior to this procedure.

these patients, however, were in the unresectable group and were subjected only to palliative procedures. Among those cases selected for pancreatoduodenectomy the gastrointestinal series were uniformly unremarkable.

A radical pancreatoduodenectomy (Fig. 5) was performed on 11 patients;[1] while 7 additional patients were subjected to exploration, biopsy, and in 5 cases a decompression of the biliary system.

The postoperative mortality[2] in the group undergoing pancreatoduodenectomy was 36 per cent. The longest survival was 5 years and 10 months. All patients with carcinoma of the ampulla of Vater listed in Table VI are now deceased with 2 exceptions, one of whom has survived for 4 years, and the second for 1 year following operation without apparent recurrence. The palliative procedures[3] performed on 7 patients resulted in a survival of at least 1 year in 3 cases and of 2 years in 1 case (Table VI).

The proportion of the pancreas resected in this group varied greatly but included all of the head (except in 1 case) and varying proportions of the body usually extending to the left of the portal vein. One total pancreatectomy was performed, but this patient did not survive the postoperative period. It is of interest that no patient in this group developed abnormalities of glucose metabolism, and in only 1 case[4] was the possibility of a deficiency of exogenic pancreatic resection raised. One individual in this category developed a chronic gastrojejunal ulcer, a factor in his death which occurred 5½ years following resection of the tumor.[5] A second patient, following pancreatoduodenectomy for ductal carcinoma, had a massive gastrointestinal hemorrhage 18 months after surgery from a presumed, but unproved, marginal ulcer.

Among those patients with carcinoma of the ampulla or choledochus, in whom a primary curative procedure was performed and who survived the immediate postoperative period (6 cases),[6] the average survival period was 4 years and 5 months. All of these patients had good appetites and gained weight steadily following discharge from the hospital. The average weight gain for the group was 6.6 kilo-

[1]Five of these cases have been reported previously by Child (8, 10).

[2]Including all patients not discharged from the hospital.

[3]Known to represent only palliation at the time of operation.

[4]This patient had approximately two-thirds of the pancreas removed. She had chronic, mild diarrhea and steatorrhea (by stool fat analysis) which was refractory to therapy with oral pancreatin. She was not incapacitated and "did a full day's work" for 2 years.

[5]No evidence of recurrent carcinoma was found in this patient at autopsy, 5½ years after pancreatoduodenectomy.

[6]Excluded are (a) the palliative pancreatoduodenectomy and (b) 1 pancreatoduodenectomy performed for recurrent tumor following previous local excision.

TABLE IV.—SIXTY-EIGHT CASES OF CARCINOMA OF THE GALLBLADDER GROUPED ACCORDING TO HISTORY AND PHYSICAL FINDINGS ON ADMISSION

Group	Disease process simulated	No. of cases
I	Acute cholecystitis	15
	(Tender, right upper quadrant mass; fever; mild icterus; also frequently symptoms suggestive of longstanding chronic cholecystitis)	
II	Chronic cholecystitis	22
	(Longstanding, right upper quadrant pain; attacks of nausea and vomiting; x-ray evidence of nonfunctioning gallbladder or calculi in gallbladder)	
III	Choledocholithiasis	12
	(History of chronic cholecystitis; jaundice associated with pain in upper abdomen; chills and fever—usually more weight loss than commonly associated with choledocholithiasis)	
IV	Vague abdominal complaints; weight loss; sometimes mild jaundice	7
V	Miscellaneous symptoms	12
	Painless jaundice	5
	Peptic ulcer symptoms	4
	Palpable abdominal mass	2
	Incidental operative finding	1
Total No. of cases		68

grams and the maximum 14 kilograms in the initial postoperative year. All of these patients returned to their previous employment (housework in 1 case) and worked steadily for a period averaging 3 years.

The difficulties in discovering these tumors at operation, particularly at a stage when resection is possible, are legion. Four (22 per cent) of the carcinomas of the ampulla in this series were not correctly identified at the primary laparotomy.[1] In 2 of these cases the operator, finding calculi in the common duct at exploration and believing that this was the source of the biliary obstruction, did not perform a duodenotomy. In a third case, a duodenotomy was performed, and the ampullary tumor was visualized and biopsied, but regarded as a benign process. This patient was subjected to radical resection 2 weeks later.

PATHOLOGIC STUDIES, CHANNELS OF EXTENSION, AND SITES OF RECURRENCE

Carcinomas of the gallbladder. Carcinomas of the gallbladder in this series were classified pathologically as undifferentiated (48), adenocarcinoma (14), epidermoid (4), scirrhous (1), and mucinous (1).

[1]One exploration in another clinic.

TABLE V.—OPERATIVE PROCEDURES PERFORMED ON 90 PATIENTS WITH CARCINOMA OF THE EXTRAHEPATIC BILIARY TRACT

	Carcinoma of the gallbladder	Carcinoma of the extrahepatic ducts	Carcinoma of the ampulla of Vater	Tota
Curative procedures				
Radical pancreatoduodenectomy[1]	1	2[2]	1a1[4]	
Cholecystectomy, radical[3]	13			
Cholecystectomy, simple	5			
Total curative procedures				32
Palliative procedures				
Exploratory laparotomy and biopsy	37	9	2	
Gastroenterostomy and biopsy	2	1		
Cholecystostomy and biopsy	1		1	
Choledochoduodenostomy and biopsy		1	1	
Cholecystogastrostomy and biopsy			3	
Total palliative procedures				58
Total operative cases				90
Total nonoperative cases (autopsy)	9	2	2	13

[1]Including partial gastrectomy in all cases; and cholecystectomy, splenectomy, transverse colectomy, and right hemicolectomy in addition to the pancreatoduodenectomy in 1 or more cases.
[2]Including hepatic artery resection in 1 instance.
[3]Including resection of hepatic tissue, lymph nodes, and gastrohepatic ligament.
[4]Including 1 radical pancreatoduodenectomy known to be palliative at the end of the resection.

The tumors had grossly extended into the liver in 20 cases; and separate metastatic hepatic nodules, usually in both lobes, were found in 33 cases. Positive nodes in the periportal region were found in 20 cases. Other sites of extension and metastases were myriad. In 3 cases, the patient's presenting symptoms were referable to duodenal or pyloric obstruction secondary to encroachment on these structures by carcinoma originating in the gallbladder.

Gross pathologic study of the gallbladder and other tissues removed at surgery in the patients with carcinoma (10) who survived at least 1 year revealed two types of tumors. Approximately one-half of these carcinomas were friable, hemorrhagic, "ragged" masses projecting from the mucus membrane. Microscopically these were papillary adenocarci-

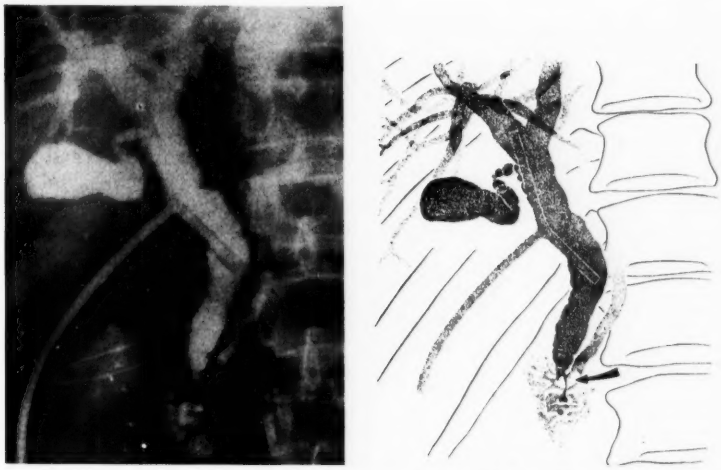

Fig. 4. N.Y.H., Case No. 618 723. Carcinoma of the ampulla of Vater demonstrated by the filling defect noted in the cholangiogram (arrow). This lesion was approximately 1 centimeter in diameter when examined following resection (pancreatoduodenectomy).

nomas. The remaining tumors were firm, discrete areas of the bladder wall with little mucosal alteration. They were described on gross section as hard, yellow-white areas of thickening of the wall, even as plaques, and microscopically as adenocarcinomatous infiltrations of the wall of the organ. There appeared to be little prognostic significance in this distinction, 2 of the longest survivors falling into the invasive group. In 9 cases the tumor was confined by the serosa of the gallbladder. In the tenth case, the cystic duct lymph node was positive for metastatic cells.[1]

An abdominal re-exploration was performed in 3 cases within 18 months of the primary resection of a carcinoma of the gallbladder. The tumor noted at these operations bore a striking resemblance to the original lesion, i.e., local recurrence at the site of the gallbladder with or without distant hepatic metastasis.

Carcinoma of the extrahepatic ducts. Tumors of the extrahepatic ducts in this group have been uniformly adenocarcinomas—usually papillary, in 1 case mucinous.

Study of the 10 autopsied cases reveals that in 3 the tumor was confined to a small area of local extension up and down the biliary ductal system (this was also apparently true in 2 unautopsied cases), death resulting from intrahepatic infection. If this local extension progressed and reached the porta hepatis (5 cases), the immediately adjacent lymph nodes were also invaded. The tumor was confined to the duct itself and to nodes in direct contact with the cystic and hepatic and common bile ducts in 7 of the 10 autopsied cases. In the remaining 3 cases the local invasion was extensive and distant metastasis had occurred.

Carcinoma of the ampulla of Vater. Tumors arising from the ampulla of Vater were uniformly well differentiated adenocarcinomas.

The development of these tumors will be described, commencing with those least extensive and progressing to those most widely disseminated. In 2 patients a local excision of a minute (less than 1 cm. diameter) tumor in the ampullary region was performed.[2] These lesions were thought to be benign, both grossly and by rapid section technique, but permanent tissue sections revealed evidence of malignancy. One of these patients was submitted to pancreatoduodenectomy 2 weeks later. No carcinoma could be found in the surgical specimen. The second was subjected

[1]This patient survived for 4 years and 4 months.

[2]One year prior to this procedure 1 of these patients was subjected to duodenotomy and inspection of the ampullary region without significant findings.

TABLE VI.—DURATION OF SURVIVAL IN PATIENTS WITH BILIARY TRACT CARCINOMA

Patients subjected to curative procedures

	Total No.	Patients discharged from hospital	Patients known to be alive following surgery					
			6 mos.	1 yr.	18 mos.	2 yr.	3 yr.	5 yr.
Carcinoma of gallbladder	19	18	14	10	7	6	5	2[1]
Carcinoma of extrahepatic ducts	2	1	1	1	1	1	1	0
Carcinoma of ampulla of Vater	11	7	7[3]	6	5	5	3	2[2]

Patients subjected to palliative procedures

	Total No.	Patients discharged from hospital	Patients known to be alive following surgery		
			6 mos.	1 yr.	2 yr.
Carcinoma of gallbladder	40	31	7	1	1
Carcinoma of extrahepatic ducts	11	6	0	0	0
Carcinoma of ampulla of Vater	7	3	3	3	1

[1]One patient is alive and without evidence of recurrence 7½ years following surgery.
[2]One of these patients developed fatal recurrence of carcinoma before the sixth year following operation. The second expired 5½ years following surgery. Autopsy revealed a gastrojejunal ulcer, and acute cholangitis; but no evidence of recurrent tumors (Child, 9, 10).
[3]Included is the 1 palliative pancreatoduodenectomy. This patient expired less than 1 year following operation.

to the same procedure 4 months following the local excision. In this operative specimen, a local recurrence with invasion of the duodenum, pancreas, and peripancreatic nodes was found.[1] These patients, of course, had no evidence of disseminated carcinoma, which was likewise true of 9 additional patients who were subjected to primary pancreatoduodenectomy. Examination of the surgical specimen in these individuals revealed a discrete noninvasive, ampullary tumor mass in 3 cases, an invasion of duodenal muscular layers but not the pancreas in 5 cases, and an invasion through the duodenal adventitia in 1 case. No involvement of the many attached lymph nodes or evidence of pancreatic invasion was found in any of these specimens. Four of these patients died within 2 months following resection, and complete autopsies were performed. No additional areas of carcinomatous tissue could be identified in any of these postmortem examinations.

One of these patients was re-explored 5 years and 9 months following the initial resection because of symptoms, and a mass of recurrent neoplasm was noted in the region of the lesser sac. No hepatic metastasis or other evidence of tumor dissemination could be found at operation. Still another patient developed a pelvic tumor 2 years and 5 months following pancreatoduodenectomy. A biopsy was performed, as this tumor invaded the vagina and was presumed to be recurrent ampullary carcinoma. The final patient in this group was autopsied 5 years and 4 months following radical resection, without evidence of any neoplastic tissue demonstrable in the cadaver at postmortem examination. Death was secondary to acute cholangiohepatitis. The 2 remaining patients of this category (primary radical pancreatoduodenectomy) are alive and without evidence of recurrence.

Among those patients treated by palliative procedures who later came to autopsy were 3 individuals with small ampullary carcinomas without demonstrable extension, who would have been candidates for pancreatoduodenectomy in the second decade of the study.

Four patients were explored and found to have hepatic metastases or extensive lymph node involvement. The ampullary mass in these cases was much larger (6 to 8 cm. in diameter) than among the previous groups and was believed by the operating surgeon[2] to represent a primary carcinoma of the head of the pancreas in each case. Two additional patients had generalized carcinomatosis (confirmed at autopsy) and were not subjected to surgery.

Four patients died during the postoperative period following radical pancreatoduodenectomy for carcinoma of the ampulla of Vater. The causes of death were bronchopneumonia (1), acute cholangiohepatitis (1), renal failure (lower nephron nephrosis) (1), and peritonitis secondary to anastomotic disruption (1). The causes of fatality among the patients subjected to palliative procedures were primarily

[1]This patient survived for approximately 18 months.

[2]The tendency of surgeons to regard the tumors in this region as primarily pancreatic rather than ampullary when they reach a certain size is noted by Cliffton in reviewing this subject.

intrahepatic infection associated with choledochal obstruction and secondarily carcinomatosis.

DISCUSSION

The greatest limitation to the application of the concept of wide local resection to these tumors is their tendency to spread rapidly and silently, to surround the celiac axis or advance to the porta hepatis (carcinoma of the extrahepatic ducts), to metastasize or extend directly to both lobes of the liver (carcinoma of the gallbladder), or to pass through the pancreaticoduodenal tissues into the retroperitoneal space (carcinoma of the ampulla of Vater). Among the 59 cases of carcinoma of the gallbladder, 40 were found to be beyond resection. Among 13 cases of carcinoma of the extrahepatic ducts, 11 were inoperable at the initial laparotomy. The ampullary carcinomas were found to be less invasive, and at surgery in 11 of the 18 cases a curative type procedure was initially believed to be feasible.

The presentation of this series of cases of carcinoma of the extrahepatic biliary tract seems justified by the fact that a large percentage (26 per cent[1]) of these patients have been treated by radical operative procedures. It was hoped 10 years ago that such an operative approach might partially alter the unfavorable prognosis traditionally associated with these tumors. The patients in this series have been followed for a sufficient period to demonstrate the minor effect on absolute curability of these procedures. At the same time it reveals that in certain instances their effect in the prolongation of survival time is of great significance.

Carcinoma of the gallbladder and extrahepatic ducts. In 1931 Evarts Graham advanced the thesis that prophylactic cholecystectomy for calculus cholecystitis was the only logical approach to the problem of biliary tract carcinoma. This suggestion was initially attacked on the premise that the operative mortality for cholecystectomy exceeded the probability of the development of carcinoma in the calculus gallbladder. It is obvious that this contention is no longer valid. In most clinics the mortality for elective cholecystectomy is now negligible. Other critics including Russell and Brown have dwelled at length on the extreme rarity of these tumors. They find the percentage of cases among general autopsy material or hospital admissions (of all ages) is small. These figures are hardly germane to the clinical problem involved. Carcinoma of the gallbladder is a disease of the aged patient. In those patients over 65 years of age with symptomatic biliary tract disease, almost 10 per cent develop biliary tract carcinoma before death.

[1]30 per cent of the operative cases.

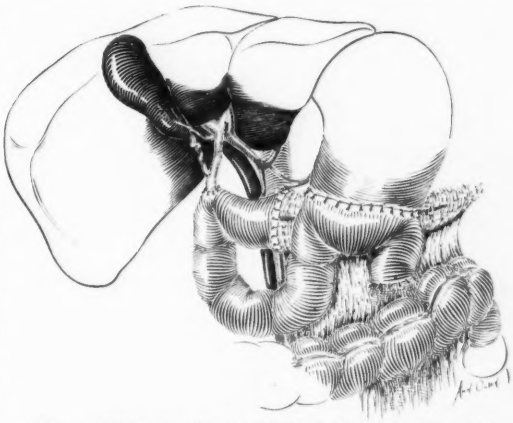

Fig. 5. The type of reconstruction of the continuity of the gastrointestinal tract employed in the present series following pancreatoduodenectomy. The gallbladder, transverse colon, right colon, and spleen were included in the resection in 1 or more instances. An intestinal loop of 25 to 30 centimeters was left between the choledochal and gastric anastomoses.

The association of biliary tract carcinoma with benign biliary tract disease, particularly with cholelithiasis, has been noted almost since the recognition of these tumors 180 years ago. Some students of this relationship have maintained that the calculi may be secondary to the obstruction produced by the neoplasm.

It is interesting to note that 5 of our patients had demonstrable gallbladder calculi for from 5 to 30 years (average of 17 years) prior to the recognition of carcinoma in that organ. Observations on the natural history of these tumors does not lead one to believe that these patients harbored carcinoma for such extended periods. Two patients in the present

TABLE VII.—DIFFICULTIES IN THE RECOGNITION OF CARCINOMAS OF THE EXTRAHEPATIC BILIARY TRACT BY THE OPERATING SURGEON

	Total operative cases	Unrecognized as carcinoma at primary procedure[1]	Unrecognized as carcinoma at secondary procedure	Unrecognized as carcinoma at a tertiary procedure
Carcinoma of gallbladder	59	7	1	
Carcinoma of extrahepatic biliary ducts	13	3	1	1[2]
Carcinoma of the ampulla of Vater	18	4	3	

[1]Three of these original explorations were performed in other institutions.
[2]Found only at postmortem examination.

series had cholecystostomies for apparent acute cholecystitis performed approximately 30 years prior to the development of carcinoma of the gallbladder.

The conclusion is unescapable that carcinoma of the gallbladder is associated with longstanding, calculus biliary tract disease. Recognition of the time when the malignant process begins is impossible. The symptoms of benign biliary tract disease continue with little change through the period in which cure or prevention is possible into the period in which resection has become impossible. The symptoms of malignant biliary tract disease are in almost all instances effectively masked by those of benign biliary tract disease.

In somewhat similar situations, in which benign and malignant processes are clinically indistinguishable, i.e., the gastric ulcer or the localized area of pulmonary atelectasis, modern thought directs an early exploration. Although the percentage of malignancy is lower in cholecystitis, the operative mortality is also lower. The prophylactic removal of all diseased gallbladders that come to the attention of the physician seems a logical solution to this problem.

Carcinomas of the gallbladder and extrahepatic ducts are at times extremely difficult to recognize at the operating table. Some of the original explorations in this series were performed in other institutions; but there is no reason to assume that they were done inexpertly. The surgeon failed to recognize the presence of a carcinoma of the gallbladder at the original laparotomy in 7 instances (Table VII), 5 of which represented cases of acute cholecystitis superimposed on a malignant lesion. In 3 additional cases (5 operations) a tumor of the biliary ducts was unrecognized at the initial procedure. The surgical impression in these cases ranged through the gamut of benign processes found in the biliary tract. In 2 instances the pathologist's rapid tissue sections confirmed a misdiagnosis of a benign process.

In the 7 patients with carcinoma of the gallbladder or biliary ducts in whom duodenal fluid was available preoperatively for study by cytologic techniques, the results were uniformly disappointing. The finding of easily distinguishable tumor cells in the bile and peritoneal fluid of these patients at operation, however, leads one to hope that this defect may be surmounted by new techniques of collection and preservation. Lemon has recently recommended immediate neutralization of the duodenal aspirate and other refinements of the collection technique.

Routine roentgenologic studies, i.e, gastrointestinal series, will usually demonstrate only the unresectable lesions in this group. Among the ductal carcinomas, the operative cholangiogram was successful in indicating the presence of an otherwise unrecognized tumor in 1 case (Fig. 3). This technique will continue to be useful and may be superseded by the preoperative "intravenous cholangiogram" which has clearly outlined the choledochus in a series of patients in whom it has been used in this center.[1]

Our studies of the results of attempts at radical resection (15 cases) for carcinoma of the gallbladder and of the surgical specimens (51) and autopsy material (17 cases) collected in this series leave small prospect of eminent substantial improvement in the prognosis of this disease attributable to radical surgery.

A study of necropsy material and operative specimens in the cases of carcinoma of the extrahepatic ducts demonstrates that these tumors remain localized for an extensive period, in many cases until death. In two-thirds of the cases coming to autopsy in this series an ap-

[1]It has not been possible to outline the choledochus in the unremitting, severely jaundiced patient with this technique, however.

parent complete removal of the tumor tissue would not have been difficult if both the hepatic artery and portal vein had been expendable. It seems probable that some form of vascular graft will ultimately make such resection a possibility.

Carcinoma of the ampulla of Vater. Although Whipple has chosen to term his own work a revival of earlier procedures, the modern era in the treatment of these tumors unquestionably stems from his description of cases treated by radical pancreatoduodenectomy in 1935 (25). At the end of the decade which followed his publication, a series of reports of radical resection for carcinoma of the ampulla of Vater, often combined with pancreatic tumors, appeared, i.e., Child (7) in 1944, Orr in 1945, Cattell (5) in 1945, Whipple (24) in 1946, and Waugh in 1946. These articles were generally optimistic in regard to the efficacy of radical resection. They noted the marked prognostic differences between ampullary and primary pancreatic lesions.

A disillusionment with radical pancreatoduodenectomy as a procedure for either cure or palliation has marked the second decade since Whipple's report, as evidenced in articles by Siler and Zinninger, by Cattell (6), and in the comprehensive review by Loggan and Kleinsasser. It is true that this has centered about the treatment of pancreatic carcinoma but the procedure itself is often indicted and the two groups (carcinoma of the pancreas and ampullary carcinoma) incompletely separated in some of these analyses. Bartlett noted no difference between these two tumor types in regard to the survival period following radical surgery. Orr (17) found the ampullary carcinomas difficult to distinguish from other tumors arising in surrounding structures. Siler and Zinninger expressed doubt that ampullary tumors were of low grade malignancy or that they metastasized late, and found the prognosis uniformly poor.

It should be noted that others have stressed the inherent differences between these tumors and justified an aggressive approach toward all ampullary lesions. Brunschwig (3) has stressed the difficulty in making a tumor type diagnosis at the operating table and believes that one must act on the assumption that any carcinoma in the region of the head of the pancreas may be a favorable type (ampullary) and should be resected as such. Within the past year Orr (18) has editorially supported the concept of radical resection of the ampullary carcinoma as a palliative procedure.

The cases of carcinoma of the ampulla of Vater in this series have been reported in part elsewhere by Child (8, 10). They have been included in this summary as, in respect to localization, tumor cell structure, and natural history, they assume greater similarity to tumors of the biliary ducts than they do to primary pancreatic neoplasms. The two longest survivors in the previously reported series from this center have recently expired between the fifth and sixth year following radical pancreatoduodenectomy. These patients were active and without evidence of recurrence for 5 years. In contrast to patients with carcinoma of the pancreas, patients with carcinoma of the ampulla receive long and effective palliation from radical resection. The diversion of the pancreatic, biliary, and gastric contents into the jejunum has not produced a high degree of invalidism in any of our patients.[1] The excellent balance studies of Wollaeger receive confirmation in the minor effect of partial pancreatectomy on these patients. In general, their nutrition has been vastly superior to a similar group following simple total gastrectomy. Their return to unrestricted employment for periods of as long as 5 years seems significant and remarkable.

The recognition of these tumors at a resectable stage is difficult and depends largely upon a policy of early exploration in cases of mild or transient obstructive jaundice and upon the lively suspicion and acute observation of the operating surgeon. Cytologic examinations of duodenal contents in this series (5 studies) have not aided in diagnosis; but improved collection techniques may make this a more useful preoperative study.

The gastrointestinal series will ordinarily reveal only the unresectable ampullary carcinomas. Operative cholangiography may demonstrate the tumor (Fig. 3) and should be

[1]Brunschwig (4) also stresses the relatively excellent nutritional status of these patients following pancreatoduodenectomy, even when the entire pancreas is removed.

employed, but cannot replace duodenotomy when an ampullary lesion is suspected. Preoperative intravenous cholangiography may help localize an incomplete obstruction of the common duct to the ampulla of Vater.

In respect to rate and type of extension, the carcinomas of the ampulla bear a striking resemblance to other tumors of localized malignancy. Extension is directed into the duodenal wall and finally through that along nerves and vessels into the retroperitoneal tissues or toward the porta hepatis. Lymph node and hepatic metastases are late developments and in some cases apparently do not occur for many years, even after the appearance of local recurrence. No novelty is claimed for this contention, which was initially ably voiced by Outerbridge in 1913 from a study of autopsy material. As he stated . . . "In most cases death results from cholaemia before metastasis or invasion of surrounding organs by the tumor has occurred." Baggenstoss made a similar, although less inclusive, observation following a study of Mayo Clinic cases in 1938. The malignant nature of this tumor is based not on its early distant metastasis (as in carcinoma of the gallbladder) but entirely on its tendency to extend to and involve the important vessels in its proximity. It thus represents a hopeful problem. In the case of other localized malignant tumors, the development of new techniques have eventually made a wide local excision possible. Many extensions of the present procedure of pancreatoduodenectomy have already been proposed, i.e., excision of portal vein by Child (11), excision of portal vein with portacaval shunt by McDermott, total pancreatectomy by Cattell (6). As Child (9) has pointed out, the result will undoubtedly be continued improvement in the operative salvage from these cases.

The threat of cholangitis following pancreatoduodenectomy, either acute (and fatal) or recurrent producing eventually fatal hepatic abscesses and biliary cirrhosis, has been recognized. Some authorities have believed that all of these patients must eventually die of intrahepatic infection and cirrhosis, if a recurrence of tumor does not interrupt the process.

Among the patients with ampullary and ductal carcinoma subjected to pancreatoduodenectomy who were discharged from the hospital and have since died, 2½, 4½, 5½, and 6 years following resection, only one attack of clinical cholangitis occurred in 1 patient.[1] The patient who expired 4½ years following resection had no symptoms of cholangitis until an extensive dissemination of recurrent tumor (ductal carcinoma) occurred which partially occluded the choledochus (autopsy). The patient surviving 5½ years was autopsied following sudden death at home and found to have acute cholangitis but no evidence of previous hepatocholangitic infection. Neither of the 2 patients in this category who are alive at the time of publication (1 and 4½ years following resection) has had symptoms suggestive of cholangitis at any time.

If the contention is true that these patients inevitably develop fatal cholangitis, it should be noted that they definitely do not follow the clinical pattern of recurrent ascending cholangitis as usually observed subsequent to choledochoplasty or Roux Y choledochojejunostomy.

SUMMARY AND CONCLUSION

A study of the 103 carcinomas of the extrahepatic biliary tract, i.e., gallbladder, biliary ducts, and ampulla, treated in this clinic during a 21 year period is presented. The influence of the adoption of a policy of radical resection on the prognosis in these patients is analyzed with the following conclusions:

In cases of carcinoma of the ampulla of Vater, pancreatoduodenectomy or similar more extensive radical resection is indicated in all individuals in whom excision of the gross tumor seems initially possible. Although the immediate postoperative mortality and complication rate is high, the palliation provided those patients who survive is longstanding and effective. Ascending cholangitis has not been a clinical problem but is the usual autopsy finding. The absolute curability is probably not greatly affected. Resections known to be palliative seem justified in selected cases.

The prognosis in patients with carcinoma of the gallbladder and extrahepatic biliary ducts

[1]This occurred 4 years after resection. The patient was asymptomatic for 2 years subsequent to this attack and then died with recurrent carcinoma (no autopsy).

is not greatly improved by the adoption of radical surgical procedures. Prophylactic cholecystectomy for all patients in the older age group with symptomatic biliary tract disease can be justified on the basis of the dangers of malignancy. This procedure appears to be the most reasonable line of approach to the problem.

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STUDIES OF BLOOD VOLUME AND TRANSFUSION THERAPY IN THE KOREAN BATTLE CASUALTY

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DURING the years 1952 and 1953 in the Korean War, there was a trend toward giving increasingly large amounts of blood throughout resuscitation. It was not unusual to administer to the critically injured soldier 15 to 30 pints of blood on the day of injury. Much of the blood was given after the control of obvious hemorrhage. The desirability of this practice was often questioned but was based on the belief that adequate resuscitation (i.e., stabilization of blood pressure and pulse rate at relatively normal levels, subsidence of clinical symptoms and signs of shock) was principally a function of restoration of blood volume. Likewise, during and after surgery, maintenance of blood volume seemed to be the most critical factor in the recovery or death of the wounded patient. The present studies of blood volume in battle casualties were, therefore, undertaken in an effort to evaluate these clinical impressions by more objective, quantitative methods, particularly with reference to the desirability and necessity for massive transfusions. All blood used in the Korean theater was either type O, banked blood or rarely, fresh compatible blood.

Several previous studies relative to blood volume following wounding have been carried out. In general, these investigations have stressed primarily the clinical status of the patient as correlated with his blood volume at the time he entered the hospital. For several reasons, we decided to place our emphasis principally on blood volume in the postoperative rather than the early resuscitative phase of the patient's course. (1) It was thought that more could be learned about the adequacy of transfusion and its effect in maintaining blood volume through resuscitation and surgery. In particular, determinations at this time would provide quantitative answers as to the necessity for large transfusions. (2) In most instances adequate hemostasis was achieved at this time allowing for adequate mixing of the labeled cells or dye without significant loss during mixing. (3) Likewise, the rapid administration of blood or colloids was not necessary here, so that mixing phenomena of labeled cells and dye could be observed without being confounded by concomitant mixing of other rapidly infusing fluids used for resuscitation.

Those patients, therefore, whose blood volumes were determined with labeled red cells were studied during the first 12 to 48 hours after surgery. When the dye T-1824 was used it was often necessary to wait until the day following surgery to avoid interfering effects due to elevated plasma hemoglobin.

METHODS

Labeled red cell method. Labeling of red cells was carried out using radioactive chromium as the tagging material. Radioactive chromium was used in preference to radioactive phosphorus because of its more lasting incorporation in the red cells. Since, with the method used, negligible escape of radioactive chromium from the red cells occurs within the first 24 hours, prolonged study of mixing could be carried out and serial volumes determined without the necessity of relabeling new cells. The following is the method used for labeling the red cells and calculating the blood volume:

1. Preparation of labeled red blood cells.
   a. Place 10 cubic centimeters of sterile, physiologic saline and 150 to 200 microcuries of radioactive chromium in a sterile, glass stoppered flask.
   b. Add 15 cubic centimeters of fresh heparinized "O" blood to the centrifuge flask.[1]

From the United States Army's Surgical Research Team of Korea, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington, D. C.

[1]Fresh labeled "O" cells were used in preference to the patient's cells so that a source of labeled cells would be readily available on short notice whenever needed.

c. Place the flask in an incubator at 38 degrees C. and allow to react for 1 hour, mixing gently every 10 minutes.

d. Wash the red cells 3 times with sterile saline.

e. Suspend the washed red cells in 2 volumes of saline and store at refrigerator temperature until ready for use.

f. If the cells are to be stored for several hours before use, resuspend in 2 volumes of plasma obtained from bank blood.

2. Red blood cell volume determination.

a. Mix the labeled red cell suspension thoroughly and aspirate into a syringe of suitable volume.

b. Place at least 2½ cubic centimeters of labeled blood from the syringe into a tared volumetric flask as a standard and weigh. Make to volume with distilled water.

c. Weigh the syringe containing the material to be injected together with the needle to be used for injection.

d. Inject the remaining labeled blood intravenously and weigh the syringe and needle immediately without rinsing.

e. Collect blood samples 20 and 40 minutes after injection and as indicated thereafter until mixing is complete. In most cases, multiple samples were taken until the counting rate of the last 2 aliquots differed by less than 5 per cent.

f. Carefully determine the hematocrit of each sample. At least 3 hematocrits were obtained on each patient.

g. Pipette 5 cubic centimeters of each whole blood sample into a counting test tube. Likewise, pipette duplicate 5 cubic centimeter samples of standard into counting tubes.

h. Count[1] all standards and samples in a well-type scintillation counter.

3. Computations.

The blood volume is calculated using the standard dilution formula $C_1V_1 - C_2V_2$ or $V_2 = \frac{C_1V_1}{C_2}$ where

C_1 = cpm/c.c. of injected material
V_1 = volume of injected material
C_2 = cpm/c.c. of patient's blood
V_2 = volume of patient's blood
In this instance:

C_1 = cpm/c.c. of diluted standard × volume to which standard was diluted / Weight of labeled blood used as standard

V_1 = Weight of syringe and needle before injections minus weight after injection
C_2 = cpm/c.c. of patient's blood after adequate time for mixing of labeled cells has been allowed
V_2 = Resultant calculated blood volume
TRCV = Hematocrit × total blood volume
Plasma volume = total blood volume minus TRCV.

[1]Standard scintillation counting techniques were used.

Dye method. When the dye T-1824 was used for plasma and blood volume determination, the technique of Gregerson and associates (4, 5) was utilized wherein 3 plasma samples were taken at 13 to 15, 30, and 45 to 60 minute intervals. The dye concentration of each sample was measured and plotted against time. The curve so obtained was extrapolated linearly back to zero time to correct for dye loss during the mixing period. This value at zero time gave the theoretical concentration of dye that would have occurred in the plasma if uniform mixing had been effected at the instant of injection and none of the dye had been excreted. When abnormal plasma hemoglobin levels or an interfering cloudiness were suspected the samples were discarded. Each reported determination was made on the basis of 3 valid samples with the exception of those so indicated where extrapolation was on the basis of only 2. When only 1 plasma level was obtained or when a linear plot did not result the observation was discarded. The total blood volume was calculated from the plasma volume and the hematocrit value. When simultaneous blood volumes were determined by using labeled cells and dye, the 2 were administered separately via different veins to avoid error through loss during changing of syringes.

In calculating the total blood volume from the plasma volume or red cell volume, no correction factors were used to offset the possible error introduced by differences between venous and total body hematocrit. The estimated normal blood volume used for the dye method was 8 per cent of body weight, and for the labeled red cell method 70 cubic centimeters per kilogram of body weight.

CONTROLS

1. Radio chromium, red cell tag.

a. Fresh red cells labeled with Cr^{51} and resuspended in 2 volumes of saline showed a transfer of 1.5 per cent of the total radioactivity to the suspending medium in 36 hours. When bank blood plasma was used for resuspension less than 0.5 per cent of the total radioactivity appeared in the supernatent fluid.

b. Counting of multiple samples of standard Cr^{51} solution, a total of 10,000 counts for each sample, gave a standard deviation of 1.6 per cent.

c. The red cell volumes of several normal individuals were determined as indicated in Table VI.

TABLE IA.—BLOOD VOLUME DETERMINED WITH RADIOACTIVE CHROMIUM

Case No.	Wt.	Ht.	TRCV		Pl. vol.		Bl. vol.		Blood rec'd (c.c.)	Per cent normal	Wounds
			c.c./K	Tot.	c.c./K	Tot.	c.c./K	Tot.			
Abdominal Wounds											
1		46		1912		2436		4346	2,000		Carbine wounds—lac. of spleen and stomach
2	74.6	38	17.4	1298	28.6	2118	46.0	3416	6,000	65	Carbine wounds entering over left inguinal ligament, perf. bladder and leaving via left buttock. Retroperitoneal muscle damage
3	72.8	46	26.4	1990	34.8	2533	60.2	4523	3,000	89	Carbine wounds entering left flank, 5 perfs. of jejunum, 2 perfs. descending colon
4	58.6	36.5	19.6	1148	36.4	2132	56.0	3280	10,500	80	Mortar—cpd. fracture rt. ileum with perf. wound of flank, buttock and rt. retroperitoneal area. Tremendous muscle destr. and hemorrhage
	58.6	38.5	23.8	1390	36.2	2221	60.0	3611	11,500	86	1 day later
5		48.5		1780		2052		3832	6,000		Mortar—extensive lac. rt. lobe of liver, perf. of ascending colon, duodenum, ileum; lac. 2 lumbar veins; perf. of diaphragm
6	66*	42.5	16.4	1082	23.6	1558	40.0	2640	500	57	Mortar—6 perfs. of ileum, fracture mid-left ileum, muscle injury to gluteus, iliacus, and psoas; 2,000 c.c. blood in peritoneal cavity
	66	43.5	27.5	1820	38.5	2540	66.0	4360	6,000	94	1 day later—postoperatively
7	63.8	68	47.1	3002	25.5	1628	72.6	4630	7,000	104	Mortar—extensive lac. small bowel and colon, requiring resection of 2 segments. Renal insufficiency, purpura, death
	63.8	68	48.7	3105	26.0	1655	74.5	4760	7,000	107	1 day later
	63.8	48	29.1	1855	34.1	2175	63.2	4030	7,000	91	1 week later
8	56.4	48	28.6	1615	33.5	1885	62.1	3500	2,000	89	Mortar penetrating pelvis dorsally—perf. of ileum in 4 places, perf. of rectosigmoid
Mean	65.4	45.8	27.1	1772	33.3	2171	60.4	3943	5,300	86.7	
Extremity Wounds											
9		41		1625		2339		3964			Mortar—perf. rt. and left thighs, left elbow, CCF rt. patella with multiple bone fragments in knee
10	60.0	31.0	16.0	962	37.4	2246	53.4	3208	2,500	76	Mortar—rt. inguinal region and rt. buttock with a large amount of muscle damage
11	95.5	43.5	27.1	2580	33.0	3128	60.1	5708	6,500	85	Mult. pen. wds. both thighs. Cpd. comm. fracture of tibia & fibula bilaterally. Traumatic amput. of rt. hand
12	72.6	40.0	19.4	1410	31.0	2250	50.5	3660	3,500	72	Mortar—CCF upper ⅓ rt. tibia. Large perf. wds. of rt. and left thighs
13	72.8	32.0	13.9	1010	31.4	2290	45.3	3300	4,250	65	CCF of left tibia and fibula with extensive soft tissue damage
14	61.3	33.0	16.0	982	34.6	2118	50.6	3100	4,500	73	CCF of rt. tibia and fibula. Perf. wound of thigh
15	76.5	32.0	16.8	1285	37.8	2895	54.6	4180	9,500	78	Traumatic severance of femoral artery and vein in midthigh (rt.). Extensive muscle damage medial rt. thigh. Subtotal severance sciatic nerve
Mean	73.1	36.0	18.2	1408	34.2	2466	52.4	3874	5,125	75	
Abdominal and Extremity Wounds											
16	72.8	51	33.7	2452	32.4	2356	66.1	4808	1,500	94	Mortar wounds—both legs. Small intrapelvic fragment at level of S_1; 5 perfs. of ileum
17*		36.0		1956		1814		2770	3,500		Multiple mortar wounds both hands, arms, and thighs; 30 perfs. of small bowel. Lac. left common iliac vein
18	71.0	43.0	23.5	1675	33.5	2380	57.0	4055	7,500	82	Artillery wounds—Traumatic amput. both arms. Mult. pen. wds. of liver. Multiple perfs. of small bowel
19*	59.6	40.0	16.7	992	26.6	1589	43.3	2581	7,000	62	Mine injury—CCF left tibia and fibula. CCF rt. tibia and fibula lower third with traumatic amput. rt. foot; large perineal wound with retroperitoneal hematoma
Mean	67.8	42.5	24.6	1769	30.8	2034	55.5	3553	4,875	79	

TABLE IA.—BLOOD VOLUME DETERMINED WITH RADIOACTIVE CHROMIUM (CONTINUED)

Case No.	Wt.	Ht.	TRCV		Pl. vol.		Bl. vol.		Blood rec'd (c.c.)	Per cent normal	Wounds
			c.c./K	Tot.	c.c./K	Tot.	c.c./K	Tot.			
Thoracoabdominal Wounds											
20	67.4	43.0	26.2	1760	37.2	2513	63.4	4273	0	91	Mortar wds. thru 10 I.S., midaxillary line of left chest, perforating diaphragm and left lobe of liver. Fragment embedded in serosa hepatic flexure
21	54.0	57.0	45.5	2480	37.9	2055	83.4	4535	7,000	120	Mortar wds.—Pen. avulsive thoracoabdominal wound, left with fracture of ribs 9 and 10, hemothorax; laceration of diaphragm, spleen, and stomach
	54.0	50.7	42.9	2320	45.7	2470	88.6	4790	7,000	127	3 days later
	54.0	41.0	28.1	1518	46.7	2525	74.8	4042	7,000	107	9 days later
22	52.2	51.0	41.6	2170	43.3	2260	84.9	4430	1,500	121	Mortar wds.—Fract. ribs 11 and 12, lac. of diaphragm ruptured spleen, hemopneumothorax
23	57	35	23.5	1340	43.7	2490	67.2	3830	2,500	96	Mortar wds.—SFW pen. rt. shoulder and entering chest. Hemothorax. Pen. wound rt. lobe of liver
	57	37	28.4	1617	48.3	2753	76.8	4370	3,100	110	2 hours later—after 600 blood with Ht. 46
Mean	57.6	46.5	34.2	1937	40.5	2329	74.7	4267	2,750	107	
Chest and Extremity Wounds											
24*	82.0	28	9.0	736	24.4	2004	33.4	2740	10,000	48	Mortar wounds—Mult. pen. wds. rt. chest, hemothorax. Mult. fragments in both thighs. Fractures of left radius, upper third left tibia, 4 and 5 metacarpals left hand
25	68.0	42	28.2	1915	39.8	2835	68.0	4750	10,000	100	Mortar wds.—Fracture of pelvis, rt. humerus compound, comm. Hemopneumothorax
26	79.5	43	23.8	1890	33.7	2290	53.0	3600	7,500	65	Mortar wds.—Perf. SFW neck and chest. Massive hemopneumothorax. Extensive lac. upper lobe left lung
Mean	76.5	37.6	20.3	1513	32.6	2376	51.4	3696	9,166	71	
Miscellaneous											
27*	50.0	43.0	28.3	1445	39.0	1915	67.3	3360	4,500	96	Mortar wds.—Right temporal wound with intracranial shell fragments and bone fragments. Severe CCF of mandible with extensive hemorrhage. CCF left humerus. SFW left knee
28	75.0	40.0	16.4	1230	26.4	1980	42.8	3210	8,500	61	Artillery wd.—CCF left temporoparietal area of skull with depression. CCF rt. femur. Compound fracture rt. radius and ulna
Mean	62.5	41.5	22.3	1337	65.4	1947	55.0	3285	6,500	79	

*In shock (also applies to Table IB).
Note: (1) The preoperative values of Case 6 are not included in the mean for the group.
(2) Only the initial postoperative volumes are included in the mean for any group.

Three duplicate determinations done several days apart gave volumes differing by 0.5, 1.7, and 4.2 per cent of the total. In each instance the second determination was made with cells that had been stored 6 hours after labeling with Cr^{51}.

2. Evans blue dye.

Nine patients who received no transfusions had multiple plasma volume determinations during their postoperative course. By using these volumes and the hematocrit to compute the red blood cell volume it was found that the results were constant within an estimated variation of S.D. = ± 5 per cent.

RESULTS

The results are tabulated in Tables I through VII.

Careful evaluation of mixing was carried out during the first 60 to 90 minutes in all patients to make sure that the volume was calculated from completely mixed samples. Samples were taken until successive counts differed by less than 5 per cent in those patients in whom radioactive chromium labeled cells were used. Furthermore, because it was suspected that relatively sequestered areas of blood might exist in some of these patients later samples were taken in 9 individuals. It was reasoned that if such areas existed and they were not completely sequestered, late samples might have mixed into larger volumes

TABLE IB.—BLOOD VOLUME DETERMINED WITH T-1824

Case No.	Date injured	Wt. (kilo.)	Hemat.	TRCV (c.c.)	Pl. vol. (c.c.)	Blood vol. (c.c.)	Blood rec'd (c.c.)	Per cent normal	Date of vol.	Est. normal (c.c.)	Wounds
Abdominal Wounds											
29	6–9	56.2	47	2150	2420	4520	5,500	101	6–10	4,500	SFW—Face, neck, eye, perf. stomach, small bowel, middle colic artery
			48	2050	2400	4450	0		6–16		
30	7–14	83.8	40	1670	2720	4390	6,500	66	7–15	6,700	Mortar wds.—Pen. wound of flank, multiple perf. of small bowel and colon, perf. of ureter, retroperit. hematoma
			39	1860	3160	5020	0		7–17		
			46	2340	2910	5250	1,000*		7–20		
31	7–28		46	2740	3490	6230	10,500		7–28		Carbine wds.—Perf. of duodenum and I.V.C. Posttraum. renal insufficiency
			47	2780	3400	6180	1,000		7–29		
32	9–2	77.6	49	2170	2450	4620	7,500	75	9–5	6,200	Machine gun—Perf. of internal iliac, arter., vein and colon
			41	2040	3190	5232	0		9–9		
Mean			45.5				7,500	80.6			
Extremity Wounds											
33	6–6		44	1780	2260	4040	4,500		6–7		Perf. fem. art. and vein, pen. wds. both lower extremities, transfns. react. 6–14 with dev. of oliguria. Blood
34	6–15	65.0	35	1230	2380	3610	7,000	68	6–16	5,200	Mortar wds.—Massive muscle wd. of thigh with cp'd commin. fract. of pelvis. Two perf. of fem. and iliac aa. Died 6–16
35	7–7	61.2	33	1010	2190	3140	4,000	64	7–8	4,900	Mine injury—Came in in shock. Traumatic amp. of left foot, macer. and fractures rt. foot
			25	940	2980	3920	0		7–10		
36	7–7	77.6	37	1800	3200	5000	7,500	81	7–8	6,200	Mine wd.—Traumatic amp. of rt. foot. Destruction of muscle of calf
			33	1850	3900	5750	0		7–10		
37	7–18	61.3	36	1400	2720	4120	8,500	84	7–18	4,900	Mine injury—Traumatic amp. left foot. Muscle destruction rt. calf
			28	1360	3640	5000	0		7–21		
			35	1650	3200	4850	1,500*		7–25		
38	7–18		34	1240	2630	3870	3,000		7–19		Mine injury—Traumatic amp. both legs at calf
			33	1540	3260	4800	1,000		7–21		
			42	2200	3300	5500	1,500		7–25		
39	8–12		40	1930	3010	4940	8,000		8–13		Mine injury—In shock on entry. Extens. cp'd commin. fracts. both tibia with traumat. amp. of left leg at calf. Rt. leg at calf incompletely amp. Massive wd. left arm and of muscle and skin of thighs. Gas gangrene. Renal insuff.
40	8–19	70.0	26	770	2380	3150	9,500	56	8–19	3,600	Artillery wds.—Massive cp'd commin. fract. both femurs and pelvis. Massive muscle destruction
			24	1010	3200	4210	500		8–20		
			52	2700	2700	5400	5,000*		8–23		
41	9–2	77.6	41	1920	3100	5080	10,500	82	9–2	6,200	Mine injury—Traumatic amp. both legs, high thigh
			44	2270	3140	5410	1,500*		9–6		
			47	2670	3260	5930	0		9–10		
42	9–6	77.6	42	1690	2570	4260	7,000	69	9–6	6,200	Mortar wds.—Traumatic amp. left leg (high calf) and rt. foot. Soft tissue wds. rt. leg
			47	1600	1900	3500	0		9–7		
			30	1480	3060	4540	0		9–10		

TABLE IB.—BLOOD VOLUME DETERMINED WITH T-1824 (CONTINUED)

Case No.	Date injured	Wt. (kilo.)	Hemat.	TRCV (c.c.)	Pl. vol. (c.c.)	Blood vol. (c.c.)	Blood rec'd (c.c.)	Per cent normal	Date of vol.	Est. normal (c.c.)	Wounds
Extremity Wounds—Continued											
43	9–20		38	600	1070	1870	12,000		9–21		Mortar wds.—All four extremities amputated. Both legs at calf and both hands
			47	1665	1880	4180	11,500		9–22		
44	9–22	70.0	38	1360	2420	3780	6,000	67	9–23	5,600	Artillery wds.—Traumatic amp. of rt. leg at knee, comp. commin. fracture left radius and ulna
			37	1320	2440	3720	0		9–24		
Mean			37.0				7,290	71.4			
Abdomen and Extremity Wounds											
45	8–4	77.6	42	1270	1750	3020	10,500	49	8–4	6,200	Perf. of TVC., small bowel, poplit. artery. In prof. shock
			45	1650	2010	3660	1,500		8–7		
			41	1410	2170	3580	1,000		8–12		
Thoracoabdominal Wounds											
46			63	2500	1630	4130	6,000		9–4		Carbine wds.—Perf. of lung, liver, stomach, diaphragm, and colon
			51	2760	2870	5630	0		9–6		
			47	2870	3520	6380	0		9–15		
Thorax and Extremity Wounds											
47	6–12	68.8	38	1350	2280	3630	16,500	66	6–12	5,500	Carbine wds.—Perf. lung rt. axill. vein and art., med. and ulnar nerve
			38	1740	2900	4640	1,000		6–14		
			42	1980	2750	4730	500		6–17		
48	7–11	83.8	40	2180	3450	5730	3,000	85	7–15	6,700	Mine injury—Perf. lung, arm, brachial plexus, cp'd fract. clavicle, small wd. of face
Mean			39				9,750	75.5			
Miscellaneous Wounds											
49	7–1	80.0	36	1970	3650	5620	4,000	88	7–2	6,400	Mortar wd.—Perf. of lung, arm, massive wound of liver
			32	1800	4000	5800	0		7–14		
			33	1360	3020	4380	0		8–7		
50	7–2		63	4080	2650	6730	6,000		7–2		Mortar wds.—Cp'd comm. wd. of mandible with destruct. of jaw. Massive hemorrhage. Devel. pulm. edema. Admitted in shock
51	8–4	80.0	52	2270	2080	4350	2,000	69	8–4	6,400	S. frag.—Perf. lung, diaphr., and liver. Massive wd. of liver. Small wds. of lower extrem. and arm
			45	2100	2600	4700	0		8–7		
52	8–26	70.5	46	2390	2920	5210		93	8–26	5,600	S.F.—Perf. of heart with peric. tamponade. Perf. of lung. Fract. 4 ribs. Perf. diaphr., stomach, small bowel, colon, spleen, left kidney. Cp'd comm. fract. left humerus, tibia
53	9–20	53.8	44	1420	1960	3380	16,000	72	9–21	4,700	Mortar wds.—Multiple wds. of small bowel, perf. of colon, liver, lung, and fem. artery. Traumat. amp. left calf at knee. Traumat. small soft tissue wds.
			40	1680	2510	4180	1,500		9–22		
Mean			48				7,000	80.5			

TABLE II.—BLOOD VOLUME AS RELATED TO TIME OF SAMPLING

Case No.	Early samples		Late samples		Diff.
	Time interval (min.)	Volume	Time interval (hr.)	Volume	
4	20, 40	3,280	1, 2	3,660	380
9	15, 30, 45	3,960	22	4,064	104
10	20, 40, 60	3,208	6, 14¾, 28	4,773	1,565
12	20, 40	3,660	1, 2½	3,660	0
18	20, 40	3,835	1, 5	4,055	220
21	40, 60	4,790	1¾	4,790	0
25	30, 60	4,400	4½, 5½	4,775	375
28	No early samples		1, 2, 5	3,210	—
17	20, 40, 60	2,770	3	3,373	603

which were not apparent in earlier samples. The results of these studies are seen in Table II. It can be seen that even though the early samples had reached a plateau and agreed with one another within less than 5 per cent, later samples taken at varying intervals revealed slightly greater apparent volumes in most instances. In all but Case 1, the later samples also fell within less than 5 per cent of one another. The interpretation of these findings is open to some question owing to the possibility of selective destruction of labeled cells. Two patients were given hexamethonium after the early mixing of labeled cells was complete. It was believed that if slowly mixing, stagnant areas of blood existed, the opening of arterioles and increased flow caused by hexamethonium might improve the circulation through such sites with more complete mixing of labeled cells therein. This process, if it occurred, would increase the measured blood volume. In the 2 instances, sufficient drug was administered to lower the systolic pressure from the range of 120 to 130 down to 90 to 100. Neither individual showed any increase in volume at intervals of 30 to 60 minutes thereafter.

The postoperative blood volume measurements revealed one outstanding result. Namely, that large transfusions were a definite necessity in many of these patients and very rarely resulted in overtransfusion. In fact, regardless of the amount of blood received, the vast majority of patients emerged from surgery with some deficit of total blood volume. Of the 25 patients studied with dye none revealed an initial postoperative blood volume greater than normal. In only 3 patients, out of 28 studied with radioactive chromium labeled red cells, was overtransfusion present, and in none of these was there any evidence of cardiorespiratory difficulty. This was probably due to the fact that the degree of overtransfusion was minimal. Two of the 3 overtransfused patients were followed with successive blood volume measurements. In one instance, the red cell volume returned to normal in 9 days and in the other 7 days. The latter's course, however, was complicated by jaundice and purpura apparently due to thrombocytopenia. Of the 3 overtransfused patients, 1 had an abdominal wound and the other 2 had thoracoabdominal wounds. They received 7,000, 7,000, and 1,500 cubic centimeters of blood respectively.

Clinical state. In general, varying degrees of hypovolemia were tolerated very well by the group during this postoperative period. Fourteen or 58 per cent of the weighed patients studied with labeled cells showed deficiencies of 15 per cent or more of the average normal for their weight. We would class this group as definitely undertransfused. The average deficiency for these patients was 32 per cent. However, of the 14 patients only 3 were in shock, these patients showing deficiencies of 38, 43, and 52 per cent respectively. The others were doing well postoperatively with no clinical evidence of shock. The average amount of blood which had been received prior to the blood volume determination in this hypovolemic group was 6,740 cubic centimeters. This figure is in contrast to the group whose deficit was less than 15 per cent. Their average replacement was 3,187 cubic centimeters or less than half that of the hypovolemic patients. The results were even more striking in the patients studied with dye. Fourteen of the 18 patients whose weights were known and whose normal blood volume could therefore be calculated revealed a deficit of greater than 15 per cent. Their average deficit was 31 per cent. All these patients were doing well postoperatively with no clinical evidence of shock. Their blood requirement pattern was similar

to those studied with labeled cells, the group with greater than 15 per cent deficit having received 7,785 cubic centimeters and the group with less than 15 per cent deficit receiving 4,160 cubic centimeters. Thus those individuals who had required the most blood remained the most hypovolemic following surgery. It was in this group that the most massive transfusions were required.

In only 1 patient did shock exist in the presence of a normal blood volume. This patient had received severe head injuries, with shell and bone fragments in the brain substance. In addition, there were severe facial injuries and a compound comminuted fracture of the left humerus. This patient had received 4,500 cubic centimeters of blood prior to the blood volume determination, which measured 96 per cent of normal for his weight. The volume was done 3 hours before his death at which time his pulse was 140–160, respiration 40–50, blood pressure 120/100 dropping to 90/70 during the succeeding hour. He died in severe pulmonary edema. The severe brain injury was undoubtedly of paramount importance here and may well explain the shock picture in the presence of a normal blood volume.

RELATIONSHIP OF LOCATION OF WOUND TO BLOOD REQUIREMENT

When the patients are placed in categories dependent upon the location of their wounds, several trends relative to blood volume and blood requirements come to light. In view of the relatively small numbers of patients, these trends must be considered tentative. They seem to be dependent primarily on one fundamental factor, the presence or absence of large areas of muscle injury. In the extremity wounds where a large amount of muscle injury was almost invariably present, large amounts of blood were necessary during resuscitation and surgery. Yet when the blood volume was determined postoperatively by either method, all members of the group fell in the hypovolemic class with deficits in volume of 15 per cent or more and an average hematocrit of 36.5. On the other hand those who had abdominal wounds, though they had received a similar amount of blood as compared to those with extremity wounds, revealed postoperative blood volumes more closely approximating normal and an average hematocrit of 45.8. The excess loss of blood from wound of muscle is easily understood when one considers the local pathologic changes involved in wounds caused by implements of war. Although there may be only a small wound of entrance, there is a large amount of destruction of the underlying muscle. This is particularly true in high velocity missile wounds. Bleeding from the large mass of damaged muscle continues from the time of injury until operation. During this time, the blood loss is greater than the observer generally realizes. The importance of other factors, such as hemolysis and trapping of blood, as added mechanisms for the causa-

TABLE III.—HEMATOCRIT CHANGES DURING RESUSCITATION, OPERATION, AND CONVALESCENCE

			Hematocrit					
Abdominal Injuries								
Patient	Admission	Postoperative	Days postoperative					
			1	2	3	4	5	6
1	32	52	38	39	39	40		
2	44	42	47	40				
3	40	—	64	62				
4	50	61	66	—	65			
5	43	45	50	55	48	47		
6	63 (albumen*)	52 (albumen*)	42	41	47	45	45	
7	34	51	44	40	43	45	45	49
8	48	—	46	—	49	43	40	39
9	—	59	52	49	45	45	43	44
10	41	43	57					
Extremity Injuries								
1	40	43	34	—	23			
2	—	41	41	39	36			
3	—	42	44	38	33			
4	36	35	35	34	29	32		
5	36	44	43	36	31	32		
6	—	47	44	37	39	32		
7	41	38 (blood)	47	42	40	36	35	
8	42	44	38	37	36	36		
9	37	35	32	31	33	33		
10	36	35	35	34	29	—	—	22

*Intravenous therapy.

TABLE IV.—COMPARISON OF SIMULTANEOUS BLOOD VOLUMES DETERMINED WITH CHROMIUM LABELED RED CELLS AND T-1824

Case No.	Cr^{51}	Dye	Diff.	Diagnosis	Per cent diff.
3	4,523	4,100	−423	(See Table I)	9.8
4	3,280	4,580	+1,300		33.1
	3,611	4,920	+1,309		30.5
5	3,832	5,700	+1,868		39.1
9	3,964	3,490	−470		12.8
10	3,208	3,995	+787		19.7
12	3,660	4,150	+490		12.6
16	4,808	5,080	+272		5.5
18	4,055	3,940	−115		2.8
19	2,581	2,680	+99		3.8
20	4,273	5,600	+1,327		26.8
21	4,535	5,540	+1,005		20.2
	4,790	5,050	+260		5.3
22	4,430	4,470	+40		.8
29*	4,071	3,860	−211		5.1

*This patient done preoperatively, therefore not included in Table I.

tion of these low blood volumes is not fully known at the present time.

Relation of hematocrit. Table III illustrates 10 patients with extremity wounds on whom serial postoperative hematocrits were done. They show a consistent fall in hematocrit. One factor which may contribute in part to this effect is the rise in plasma volume observed in many hypovolemic convalescent patients. A rising plasma volume and falling hematocrit were noted in the absence of any significant change in the total red cell volume which observation indicated a dilution effect as being at least partially responsible for the falling hematocrit.

As has been previously reported, hemoconcentration characteristically follows severe intra-abdominal injuries (1). This is probably due to the loss of plasma in excess of red cells into the bowel wall, mesentery, and peritoneal cavity. Serial postoperative hematocrits in patients with abdominal injuries, as compared with the postoperative changes following wounds of the extremities, are seen in Table III. Because hemoconcentration and plasma loss were so frequently quite marked, surgeons often administered dextran as an adjunct to blood transfusion therapy during and after repair of major intra-abdominal injuries. This was true during much of the current observation.

Comparative blood volumes. In 15 patients, simultaneous blood volume determinations were carried out using labeled red cells and T-1824. The results are recorded in Table IV. In general the methods agreed fairly well, the average difference being 16.3 per cent and falling in the range of difference found by previous investigators in normal individuals. In 3 patients (20 per cent), however, the discrepancy was considerably larger (26 to 39 per cent), the dye volume being larger in all instances. All 3 of these individuals had severe abdominal wounds, 2 of the 3 having lacerations involving the liver. This would suggest that the same factor causing hemoconcentration in such patients allows for leakage of dye out of the vascular system with resultant falsely high plasma and blood volume determinations. Peters has commented previously on the loss of the dye, T-1824, from the blood stream particularly in the liver vasculature. The involvement of the liver in 2 of these 3 cases is, therefore, of added interest and significance. These data suggest that under certain circumstances the dye method may not be a reliable one.

DISCUSSION

The impression was originally gained by those in the North African-Mediterranean Theater (1) that blood loss rather than any other factor was responsible for shock in the wounded patient. Their findings indicated that the presence or absence of shock as well as its degree upon admission to the hospital was directly correlated with the deficiency in blood volume present at that time. The present studies lend support to these findings and extend the concept to the surgical and postoperative period where it is seen that tremendous amounts of blood are often necessary to maintain the blood volume close to normal range. Of the 53 patients studied, 31 or 59.6 per cent required over 10 pints of blood. In other words, over half of the patients studied required complete replacement of their blood volume. Of these 31, 9 required 20 pints or

roughly twice their blood volume. This group emphasized well the real necessity in some patients for massive transfusions. The average deficiency of blood volume in these 31 individuals after receiving such massive transfusion was still 25.2 per cent.

In addition to the problem of how large a circulating blood volume was necessary for these patients was that of how effectively the blood transfused had increased that volume. Possibly present in almost every patient observed but becoming more apparent with the larger volumes of transfusion, was an apparent discrepancy between the amount of blood transfused and that actually measured after operation. This volume deficit appears to consist of both plasma and red blood cells. As examples the data of Table V were extracted from Table I and arbitrary estimates of admission blood volume made. Most of these patients were chosen as examples because the volumes involved were large enough to make errors in estimation of initial volume relatively insignificant. They demonstrate an average deficit of 5,373 cubic centimeters with a range from 1,600 to 7,900 cubic centimeters. Likewise 10 patients requiring postoperative transfusions were studied with one or more determinations of their plasma volume with Evans blue for up to 7 days after wounding. The results are tabulated in Table VII. When a transfusion intervened, between 2 determinations the change in circulatory red cells measured was significantly less than that expected in 6 of 12 instances. In none of these patients was there clinical reason to suspect red cell loss.

It was because of these consistently low blood volumes after large transfusion and the discrepancy between the volume of blood infused and that measured thereafter that such concern was shown over the possibility of incomplete mixing of labeled cells in relatively sequestered areas of blood volume. If large amounts of blood were pooled in areas relatively inaccessible to mixing, falsely low total blood volumes would be the result. Although the blood volumes calculated from late samples were slightly greater than those calculated from early ones, in no instance did they result in a blood volume of 5,000 cubic centimeters or over. One of the 9 patients showed an increase of 1,565 cubic centimeters in blood volume as calculated from the late samples. He had previously been resuscitated with only 2,500 cubic centimeters of blood. The remaining 8 patients received 10,500, 10,000, 8,500,

TABLE V.—SHOWING DISCREPANCY BETWEEN BLOOD RECEIVED AND BLOOD VOLUME THEREAFTER

(a)	(b)	(c)	(d)	(e)	(f)	(g)
Pt. No.	Wt. (kgm.)	Estimated B.V. on admiss. (c.c.)	Vol. transfused (c.c.)	Postop. B.V. (c.c.)	Deficit (c.c.)	Remarks
30	84	2,700	6,500	4,400(*)	4,800	Abd. wound
32	78	2,500	7,500	4,600(*)	5,400	Abd. wound
34	65	2,100	7,000	3,600(*)	5,500	Ext. wound
37	61	2,000	8,500	4,100(*)	6,400	Ext. wound
38		2,500	3,000	3,900(*)	1,600	See note(§)
41	78	2,500	10,500	5,100(*)	7,900	See note (§)
5		2,500	6,000	3,800(o)	4,700	Abd. wound
11	96	3,000	6,500	5,700(o)	3,800	Ext. wound
15	76	2,500	9,500	4,200(o)	7,800	Ext. wound

(c) Estimated as 40 per cent of normal.
(d) Volume of whole blood received during resuscitation and operation.
(e) The circulating blood volume measured several hours to 1 day after operation.
(f) Columns c and d less column e.
(*) Measured with Evans blue and hematocrit.
(o) Measured with Cr^{51} and hematocrit.
(§) These patients entered with tourniquets in place above traumatic amputations and underwent uneventful amputations with minimal blood loss and had thereafter only the clean amputation wounds.

TABLE VI.—RED CELL VOLUMES AS DETERMINED WITH RADIOCHROMIUM

Normal Subjects

(a)	(b)	(c)	(d)	(e)	(f)
Date	Subj.	Wt. (kgm.)	Hct. (per cent)	RBCV, predicted normal (c.c.)	RBCV measured (c.c.)
12- 2	A	51	42	1600	1780 (female)
12- 6			40		1750
12- 4	B	89	45	2750	1900
12-11			40		1820
12- 7	C	65	44	2000	2560
12- 9	D	71	44	2200	1860
12-13			45		1870
12-11	E		46		2180

(d) Hematocrit determined on the specimens taken for Cr^{51} determination.
(e) Red blood cell volume expected on the basis of 30 c.c./kgm. body weight.
(f) Red blood cell volume measured.

TABLE VII.—RED BLOOD CELL VOLUME RESPONSE TO TRANSFUSION, MEASURED WITH EVANS BLUE

(a)	(b)	(c)	(d)	(e)	(f)
Case No.	RBC rec'd (c.c.)	ΔRBC observed (c.c.)	ΔRBC-RBC rec'd (c.c.)	Per cent of RBCV	Per cent of RBC rec'd
Fresh Blood Received					
47	450	+390	−60	4.0	−13
	225	+240	+15	0.8	+6
30	450	+480	+30	1.7	+6
37	675	+290	−385	28	−58
38	450	+300	−150	10.8	−33
	675	+660	+15	0.8	−2
40	2250	+1710	−540	36.0	−23
41	675	+350	−325	16.0	−48
Bank Blood Received					
31	450	+210	−240	3.9	−53
40	225	+230	+5	0.5	+2
53	675	+260	−415	37	−62
43	675	+1065	+390	35	+58

(b) Red cells received by transfusions between measurements of the plasma volume.
(c) The change in red cell volume as measured by plasma volume and hematocrit determinations before and after transfusion.
(d) The difference between columns (b) and (c).
(e) Column (d) expressed as per cent of the total measured red cell volume.
(f) Column (d) expressed as per cent of the transfused red cell volume

7,500, 7,000, 3,500, and 3,500 cubic centimeters respectively, and the blood volume increase when calculated from the late samples as compared with the early samples was 600 cubic centimeters or less in every instance. Likewise in the 2 patients given hexamethonium no increase in blood volume occurred concomitant with the fall in blood pressure. Furthermore, in those patients who had received massive transfusion and survived, none developed clinical or laboratory evidence of overtransfusion during their postoperative course. If such a pooling mechanism as has been postulated existed early, one would expect a reversal of this process during clinical recovery with mobilization of substantial amounts of trapped blood and some resultant evidence of overtransfusion. In no instance did such occur. Although these data are not sufficient for positive conclusions, they do not support the concept that a significant amount of pooling existed in these patients receiving massive transfusions.

Further answers to this question might be obtained by two approaches. (1) Weigh the patient on an accurate scale when he enters the hospital. When resuscitation and surgery are completed, weigh again and determine the blood volume. Where such large volumes of infused blood are involved, one should see significant gains in weight if most of the blood has been retained; little or no change if it is being lost externally as fast as it is being infused. Correlating the postoperative blood volume with change in weight would thus help clarify the question of loss versus pooling. Obviously if most of the bleeding was into the tissues little would be learned by this procedure. (2) Determine the blood volume postoperatively with chromium labeled cells. Determine the hemoglobin to radioactive chromium ratio in blood and in tissue biopsies such as muscle. If large amounts of blood are sequestered in the tissue and inaccessible to the labeled cells, the hemoglobin to chromium ratio will be increased considerably in the tissue.

The quality of bank blood used for transfusion was investigated by Crosby and so far as indicated by the indices used (plasma hemoglobin, plasma potassium, and osmotic fragility) this blood was comparable to that available in the United States.

Investigations by means of the Ashby count, as reported previously by Crosby, indicate that in a small portion of A, B, and AB recipients receiving large amounts of O blood there will be a destruction of the patient's own cells extending over several days, but this is relatively infrequent and usually involves volume changes much smaller than those reported here.

The relative importance of hemolysis of recipient and donor cells as a contributing cause for the large requirement of blood replacement in these patients is not fully known at the present time. These patients do not show overt clinical manifestations of rapid blood destruction such as chills, fever, and jaundice. Moreover the average plasma hemoglobin done immediately after surgery in 22 patients who had received an average of 12 pints

of blood each day was only 18 milligrams per cent (normal 5 mgm. per cent). Since the intravenous infusion of 10 to 16 grams of hemoglobin (equivalent to hemolysis of 60 to 100 c.c. of blood) in normal individuals will induce plasma hemoglobin levels of greater than 300 milligrams per 100 cubic centimeters, as pointed out by Gilligan and Ottenberg and their associates, the levels found in these postoperative patients would be indicative of minimal intravascular hemolysis. The rate of plasma hemoglobin clearance is of course a factor here. The most rapid clearance rate found in the group studied was 5 milligrams per 100 cubic centimeters per hour which would be insufficient to lower a significantly high concentration of hemoglobin to the levels found even over a period of many hours. Likewise the bilirubin levels observed by Scott and associates in a similar group of patients would correspond to a relatively small degree of blood destruction. The rate of plasma clearance, principally by the liver, is again a critical factor here and the necessary data for such evaluation in these patients are not at hand. The infusion of 16.4 grams of hemoglobin by Ottenberg and Fox (equivalent to hemolysis of approximately 100 c.c. of blood) in a normal individual resulted in a plasma bilirubin concentration of 1.4 milligrams per cent 10 hours later, with a gradual fall thereafter and remaining greater than the preinjection level 24 hours later. Clearance of bilirubin in the wounded patient, where impaired hepatic function has been shown by others, would be expected to be slower than in normals. Therefore, the 6 hour postoperative average level of 2.5 milligrams per cent, which is the highest level reached in any of the preoperative and postoperative specimens, would imply relatively small amounts of hemolysis.

The postoperative hematocrit afforded a relatively poor index to the requirements for transfusion. Because of rapid changes in plasma volume which take place independently from changes in red cell volume after extensive blood loss, the hematocrit gives little information about the actual red cell volume at any given time, and conclusions concerning the status of total blood volume drawn from hematocrit data alone may be in error

CONCLUSIONS

Blood volume determinations have been carried out postoperatively in 53 wounded patients. These patients required large amounts of blood to maintain them through the phases of resuscitation and surgery. Generally extremity wounds, in which large amounts of muscle destruction had taken place, required the largest amounts of blood and still remained the most hypovolemic following surgery. However, no matter where the injury was located, if considerable areas of muscle were involved large amounts of blood were usually required.

Overtransfusion occurred in only 3 instances and in no case was it of sufficient degree to cause cardiorespiratory symptoms. The error in most cases was undertransfusion rather than overtransfusion.

Hematocrit determinations in the postoperative period are not a reliable index to the requirement for blood.

Where simultaneous blood volumes were determined with labeled cells and dye, the difference between the 2 was 16 per cent, the dye volume being greater in all but 4 instances. However, in severe abdominal wounds, especially with liver involvement, the discrepancy was much larger. Here the dye volumes were greater by 26.8, 33, and 39 per cent. This probably represents increased capillary permeability as well as gross vascular damage in the involved area with resultant leakage of dye.

The discrepancies between the large amounts of blood given and the small blood volumes determined thereafter are explainable on 3 possible bases: (1) trapping of large amounts of blood in a sequestered state which mixes slowly or not at all, (2) hemolysis of large amounts of donor or recipient erythrocytes, (3) continued loss of blood either externally or into the tissues during the preoperative, operative, and postoperative periods. The latter is believed, at the present time, to be the most important of these factors.

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PROGNOSIS IN CANCER OF THE UTERINE CERVIX BASED ON THE VAGINAL SMEAR BEFORE TREATMENT

SR—The Sensitization Response

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THE rational selection of treatment for the patient with cervical cancer is an objective that has never been satisfactorily realized. When radiotherapy won an established position 40 years ago, a choice between surgery and irradiation was presented. At that time, radiation displaced surgery and became the standard treatment because a higher proportion of over-all patients was cured with less risk than by excision. In the last 15 years, the risk and morbidity of radical surgery have been brought down to the range of irradiation, and the survival rate in these selected cases is impressive.

At the present time, either radiation or surgery is effective in a significant number of cases of cancer of the cervix, and the choice of treatment depends primarily upon the inclination of the therapist. The clinical stage of the tumor is a useful guide in that the more advanced lesion is probably less suitable for radical hysterectomy, but even this guide is coming to have less importance since the introduction of ultraradical surgery. A method for precise individual selection has been absent. From evidence reviewed here, this impasse may be broken. Recognition of the treatment most suitable for the individual patient with cancer of the cervix may now be possible.

Characteristic changes in the benign basal cells of the vaginal smear indicate whether or not the patient's tumor will respond favorably to irradiation.

Some patients with cancer of the cervix exhibit cells in the vaginal smear that are unlike those in the normal. The alteration is a cytoplasm that is finely vacuolated and simultaneously increased in density. It stains a deep lavender with Papanicolaou's polychrome stain. These changes are principally found in the basal cells (called transitional cells in histologic terminology) but occasionally in the precornified cells as well. It is called the sensitization response, or SR, because when present the tumor and the patient are usually sensitive to irradiation.

In some patients SR is prominent; in others, it is absent. A quantitative estimate is arrived at by differentially counting 100 consecutive nonmalignant epithelial cells. The number of cells showing SR is expressed as a percentage. From an analysis of the cases, when the significance of this phenomenon was first recognized, 10 per cent was regarded as the critical level. Patients whose smears showed 10 per cent or more of the cells with SR are said to have marked SR. Those in whom no more than 9 per cent of the benign epithelial cells show SR are classified as poor SR.

In 136 patients with cervical cancer treated radiologically and followed for 5 years the pretreatment vaginal smears have been analyzed for SR (Table I).

There are only 35 stage I cases because many of the patients of this stage were treated surgically. The cure of 7 patients out of 12 with marked SR is only modestly better than 6 out of 23 with poor SR. The salvage in the marked SR group is impaired by the loss of 3 patients from radiation damage. In stage II there are 65 patients, 30 of whom had marked SR, and of these 24 (80 per cent) survived, while of the 35 who had poor SR, only 8 (23 per cent) survived for 5 years. In stage III there were 28 patients, only 8 of whom had

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TABLE I.—SR IN PATIENTS TREATED RADIOLOGICALLY—5 YEAR RESULTS

	Cases No.	Cures No.	Cures Per cent
10 per cent or more SR			
Stage I	12	7	
Stage II	30	24	
Stage III	8	6	
Stage IV	1	0	
	51	37	73
9 per cent or less SR			
Stage I	23	6	
Stage II	35	8	
Stage III	20	1	
Stage IV	7	0	
	85	15	18

marked SR, but of these 6 lived. By contrast, only 1 of the 20 patients with poor SR was saved. Of the 8 patients in stage IV, only 1 had good SR, and none of the cases survived. Of the entire number, 51 had marked SR and 37 (73 per cent) of these survived. Of the 85 patients with poor SR, only 15 (18 per cent) survived. Thus a consistently better survival is noted in patients with marked SR treated by radiation.

An unexpected finding is a reverse correlation in the surgically treated cases (Table II). Though poor SR is associated with a poor prognosis in stage I and II lesions treated radiologically, quite the opposite—a good prognosis—is found if lesions of the same extent with poor SR are treated surgically. Of 80 patients with poor SR in whom a radical hysterectomy was done, 57, or 71 per cent, survived for from 2 to 5 years. In contrast, of 58 patients with poor SR treated with radiation, only 14, or 24 per cent, survived 5 years. Thus we have two groups of patients with the

TABLE II.—SR IN PATIENTS TREATED WITH RADICAL HYSTERECTOMY AND REGIONAL LYMPHADENECTOMY—2 TO 5 YEAR RESULTS

	Cases No.	Cures No.	Cures Per cent
10 per cent or more SR			
Stage I	12	7	
Stage II	11	2	
	23	9	39
9 per cent or less SR			
Stage I	62	46	74
Stage II	18	11	61
	80	57	71

same clinical extent of disease, with the *same* cytologic picture before treatment, yet the survival rates are significantly different in the two methods of treatment. Such figures as these suggest that the patient with poor SR and a stage I or II cancer of the cervix would be better treated surgically than by radiation.

How well do the patients with marked SR do if treated surgically? We have already indicated that such patients, when treated by radiation, have a rather high survival rate, for of 42 patients classified as stage I and II with good SR, 31, or 74 per cent, survived 5 years. However, if cases with the *same* clinical stage and the *same* cytologic picture of marked SR are treated surgically, the results are quite different. The survival rate is roughly half that of the radiated cases. Twenty-three patients with good SR had radical hysterectomies and 9 survived, 39 per cent. These figures would appear to indicate that for the stage I or II patient with marked SR cytologically, the treatment of choice is radiation, rather than radical surgery.

The figures just quoted are derived from those in Table III where the cases are placed in three categories; i.e., poor SR is subdivided into those with less than 1 per cent SR called no SR and 1 to 9 per cent SR called modest SR. For patients with no SR the cure rate with surgery is 72 per cent and with radiotherapy is only 17 per cent. Those with modest SR occupy an intermediate position. This graduated influence of SR in patients treated in either manner is in keeping with standard biologic behavior. The figures in Table III are arranged so that these trends can be seen. It may also be noted that SR has prognostic significance only if the form of treatment is considered. If the survival rate of *all* cases with marked SR is compared to the survival rate of *all* cases with no SR without taking into consideration the kind of therapy, there is no difference. Fifty-five per cent of the patients with no SR survived and 62 per cent with marked SR. Thus, if we consider the cytologic picture without any regard to therapy, we find no significant difference. The two groups cancel one another. The patients with poor SR raise the cure rate of patients treated surgically. The differences disappear if

just over-all survivals are considered in relation to the cytologic picture.

Let us then consider stage of disease in relation to type of therapy. In these series there were 29 patients of stage II treated surgically of whom 13 survived—a survival rate of 45 per cent ± 9.2. There were 65 patients in stage II treated radiologically; of these, 32 survived, or 49 per cent ± 6.3. At first glance, radiation might appear to be slightly better, but when the standard error is considered, it is apparent that there is no real difference between the two groups.

Thus, if we consider the cytologic picture without regard to the form of therapy, it appears of little importance. On the other hand, if we consider the specific therapy and ignore the cytologic picture, we find no difference in survival, but there are real differences. The difficulty is that they are not readily apparent. It is only when we consider the cytologic picture *and* the type of therapy that real differences appear.

To return to the 29 stage II patients treated surgically, if we consider what specific cytologic picture was present, we find that 11 of the 13 patients who survived (85 per cent) had poor SR. In the 65 patients treated radiologically, there were 33 deaths, and, of these, 27 (82 per cent) had poor SR. Here is a definite, distinct difference, which only becomes visible when both the cytologic picture and the type of therapy are taken into consideration.

For more than a generation, there has been an unending controversy as to which method of treatment was superior in cancer of the cervix. There are the strong advocates of radical surgery and the equally strong advocates of radiation therapy. From the figures just quoted we would appear to come to the fortunate conclusion that both methods are superior. Either method will produce superior results in a certain group of patients. The patient with marked SR does well if treated by radiation and poorly if treated by surgery. The stage I and II patient with poor SR does well with surgery and badly with radiation.

It must not be assumed from the previous discussion that stage III and IV cases can be considered in the same light as the stage I and II cases. In the more advanced cases we may be dealing with a different problem. In the patient whose lesion clinically is a stage III and who has no SR, there is no way of knowing whether she had SR at one time and all evidence of it has disappeared, or whether it was ever present. This is a more complex situation, and one that cannot be discussed satisfactorily because of the paucity of information. Radiotherapy is more effective in the advanced case with SR than in those cases without SR. However, there are no surgical data for comparison.

TABLE III.—STAGE I AND II—CANCER OF THE CERVIX

	0 per cent SR		
	Cases No.	Cures No.	Per cent
Surgery	65	47	72
Radiation	30	5	17
	95	52	55
	1 to 9 per cent SR		
Surgery	15	10	67
Radiation	28	9	32
	43	19	44
	10+ per cent SR		
Surgery	23	9	39
Radiation	42	31	74
	65	40	62

If the phenomenon of SR is to become generally available and useful, it must be reproducible. Its recognition by technicians of limited training is desirable. In order to evaluate the reproducibility of SR, slides from 50 patients were examined as unknowns by 10 observers of varying experience, in our laboratory. Their backgrounds in cytology ranged from 11 years to only 3 months.

The 50 patients treated radiologically, referred to in Table IV, were equally divided into 25 who lived 5 years without evidence of disease, and 25 who died within that interval. Consecutive cases with a pretreatment slide that was good enough to allow 100 epithelial cells to be counted were used. Excluded were those patients dying of radiation damage or intercurrent disease.

The differential count in each case was correlated with the clinical course. If 9 per cent or less SR was counted and the patient died, it was called correct; if the patient lived, the count was called a mistake. If 10 per cent or

TABLE IV.—SR IN PRETREATMENT SMEARS ON 50 CASES OF CANCER OF CERVIX TREATED RADIOLOGICALLY AND FOLLOWED 5 YEARS

Observer	Experience	25 Survivals		25 Deaths		No. correct in predicting outcome	Per cent correct
		10 per cent or more SR	9 per cent or less SR	9 per cent or less SR	10 per cent or more SR		
I	11 years	22	3	25	0	47/50	94± 3.4
II	6 years	16	9	23	2	39/50	78± 5.8
III	3 years	19	6	24	1	43/50	86± 4.9
IV	2½ years	17	8	24	1	41/50	82± 5.5
V	2½ years	17	8	21	4	38/50	76± 6.0
VI	1 year	19	6	21	4	40/50	80± 5.7
VII	1 year	17	8	21	4	38/50	76± 6.0
VIII	6 months	20	5	23	2	43/50	86± 4.9
IX	5 months	18	7	18	7	36/50	72± 6.3
X	3 months	16	9	23	2	39/50	78± 5.8

more SR was counted, it was called correct if the patient lived and a mistake if she died. It may be seen that the accuracy ranged from 72 to 94 per cent. In general, the more experienced and proficient observers attained a better score, but even the comparative newcomers did fairly well.

Because SR is manifested principally in the basal cells, one would expect it more frequently in the postmenopausal group. This trend is evident in a general way. Of the 136 patients referred to in Table I, 74 were 51 years of age or older and 62 were 50 or younger (Table V). SR was present in 32 of the 74 postmenopausal patients (43 per cent) and in 19 of the 62 premenopausal patients (31 per cent). Thus the incidence of SR is slightly higher in the postmenopausal group, but this difference is not great enough for the age of the patient to give a definite clue as to the possibility of the presence of SR.

The recognition of SR requires a moderate amount of special training. If a simpler index could be found it would be of obvious advantage. Because SR occurs in basal cells with few exceptions, it was suggested that perhaps the proportion of basal cells present would have a similar connotation. The incidence of basal cells was determined by differentially counting 100 benign epithelial cells,

TABLE V.—RELATION OF AGE, SR, AND 5 YEAR SURVIVAL IN PATIENTS TREATED RADIOLOGICALLY

Stage	9 per cent or less SR				10 per cent or more SR			
	Age, 50 years or less		Age, 51 years or more		Age, 50 years or less		Age, 51 years or more	
	Cases No.	Cure No.	Cases No.	Cure No.	Cases No.	Cure No.	Cases No.	Cure No.
I	5	0	18	6	6	5	6	2
II	24	5	11	3	12	11	18	13
III	12	1	8	0	1	1	7	5
IV	2 / 43	0 / 6 (14%)	5 / 42	0 / 9 (21%)	0 / 19	0 / 17 (89%)	1 / 32	0 / 20 (62%)
II, III, IV*	38	6 (16%)	22	3 (14%)	13	12 (92%)	26	18 (69%)

*Stage I cases are excluded from the total in this line in order to evaluate better the distribution of patients by age, because many of the younger in the Stage I group were treated surgically.

TABLE VI.—BASAL CELL COUNTS ON PRETREATMENT SMEARS IN 50 CASES OF CANCER OF THE CERVIX TREATED RADIOLOGICALLY AND FOLLOWED 5 YEARS

Observer	Experience	25 Survivals		25 Deaths		No. correct in predicting outcome	Per cent correct
		10 per cent or more basal cells	9 per cent or less basal cells	9 per cent or less basal cells	10 per cent or more basal cells		
I	11 yr.	22	3	22	3	44/50	88± 4.6
II	6 yr.	17	8	23	2	40/50	80± 5.7
III	3 yr.	24	1	21	4	45/50	90± 4.2
IV	2½ yr.	21	4	21	4	42/50	84± 5.1
V	2½ yr.	21	4	19	6	40/50	80± 5.7
VI	1 yr.	24	1	19	6	43/50	86± 4.9
VII	1 yr.	23	2	18	7	41/50	82± 5.5
VIII	6 mos.	23	2	20	5	43/50	86± 4.9
IX	5 mos.	21	4	18	7	39/50	78± 5.8
X	3 mos.	21	4	21	4	42/50	84± 5.1

placing them in 3 categories—cornified, precornified, and basal cells. The number of basal cells expressed as a percentage was used. Again the line was drawn at 10 per cent; i.e., 10 per cent or more and 9 per cent or less.

The group of 50 patients treated radiologically in whom a pretreatment smear was evaluated for SR by 10 observers was similarly evaluated by basal cell counts. These were done as unknowns and actually were counted simultaneously for basal cells and for SR. The results are tabulated in Table VI. The accuracy ranged from 78 to 90 per cent. The observers' experience appeared to be of little consequence in this evaluation, for some of those with limited proficiency did as well as those highly skilled, which is in keeping with the simplicity of the technique.

In the 136 patients treated radiologically referred to in Table I, basal cell counts have been done in all. In Table VII the correlation of basal cells and 5 year cure is presented. There is a consistently higher salvage rate in those with many basal cells than in those with few. This difference is most marked in stage II where a cure rate of 64 and 31 per cent respectively is noted. The over-all cure rate of 26 per cent in those with few basals and 49 per cent in those with many basal cells is not as striking a difference as seen in SR, but it is distinctly similar.

In those patients treated surgically, the proportion of basal cells appears to be of less significance (Table VIII), for in stage I there is no difference in the salvage rate between those with many and those with few basal cells. However, in stage II results were rather poor in those patients with many basal cells, as only 1 of 10 was cured, thus confirming the same general trend as SR.

One would expect that basal cells would correlate more closely than SR with age, and indeed this is found to be true, but the correlation is by no means absolute, for if one looks at the figures in Table IX excluding stage I cases, one finds that two-thirds of the older age group have many basal cells and that only two-fifths of the younger patients have 10 per cent or more basal cells.

DISCUSSION

The consistent correlation of good SR with survival in patients treated radiologically first

TABLE VII.—BASAL CELLS IN PATIENTS TREATED RADIOLOGICALLY—5 YEAR RESULTS

	Cases	Cures	
	No.	No.	Per cent
10 per cent or more basal cells			
Stage I	20	8	40
Stage II	36	23	64
Stage III	14	5	
Stage IV	4	0	
	74	36	49
9 per cent or less basal cells			
Stage I	15	5	33
Stage II	29	9	31
Stage III	14	2	
Stage IV	4	0	
	62	16	26

TABLE VIII.—BASAL CELLS IN PATIENTS TREATED WITH RADICAL HYSTERECTOMY AND REGIONAL LYMPHADENECTOMY—2 TO 5 YEAR RESULTS

	Cases	Cures	
	No.	No.	Per cent
10 per cent or more basal cells			
Stage I	16	12	75
Stage II	10	1	—
	26	13	50
9 per cent or less basal cells			
Stage I	58	41	71
Stage II	19	12	63
	77	53	69

drew our attention to this phenomenon. The initial published series of 100 cases had a cure rate of 66 per cent in those with marked SR and of 18 per cent in those with poor SR (3). The corresponding figures of 73 and 18 per cent in the present series after the addition of 36 more cases re-enforces the statistical validity of this observation.

The finding that marked SR has the opposite connotation in patients treated surgically was entirely unexpected, but nonetheless definite. It must be kept in mind that the surgical cases are all comparatively limited clinically; i.e., stages I and II. Marked SR in these cases may only be an index of the extent of the disease or velocity of its growth. This concept is supported somewhat by the observation that stage I and II patients with marked SR have a 64 per cent incidence of regional node metastases to be contrasted with a 17 per cent node involvement in patients with poor SR (2). This fact may explain in part the unsatisfactory results in patients with marked SR when treated surgically and the much better results if poor SR is present.

The 2 to 5 year cure rate given here in the surgical series is presented less favorably than it really is, for it includes 4 patients living and well when last seen, all of whom had good SR and developed a recurrence which was successfully treated radiologically. In the present discussion, all of these are called surgical failures and are not listed as cured.

SR has been independently observed by others; for example, Kjellgren and Fredrikson of Gothenburg, Sweden; but it has not been applied very widely. The evaluation of the same set of slides by 10 observers was arranged in order to test its reproducibility. The finding of an accuracy of 72 per cent in the poorest score of one of our newest students is reassuring. The fact that the best score of 94 per cent is superior to the recorded series in Table I is to be explained on two counts. All of the 50 smears referred to in Table IV were good technical preparations, where 100 epithelial cells could be counted in a reasonable period of time. Many of the smears on the 130 patients noted in Table I were of poor technical quality; enough epithelial cells individually displayed and properly stained were found only with difficulty after a tedious search. It has been customary in the past to take only 1 slide prior to treatment for the diagnosis of cancer. We now take several smears before treatment so that a suitable one may be available. The second factor of selection in the series of 50 cases, as mentioned earlier, is the exclusion of deaths due to intercurrent disease and of 3 patients, all of whom had marked SR and died of radiation damage.

Although SR occurs more frequently in the older woman with cancer of the cervix, it is by no means a function of age. Fully half of the older group lack marked SR, and a generous quarter of the younger ones have marked SR. It is of interest that marked SR in the younger group carries an even better prognosis in radiotherapy than it does in the older patient. Unfortunately the numbers are small; however, this concept is supported by Glucksmann's finding that changes in the nonmalignant tissue in biopsies taken during radiation may be significantly correlated with prognosis only in the younger patient.

SR requires a certain amount of special training and knowledge of cytology, that is not generally available. A cheaper method that could be done by those without any training was sought in the basal cell counts. It was found that evaluation of the smear for the proportion of basal cells could be done with a high degree of uniformity that was not influenced by the cytologic proficiency of the 10 observers tested. In the series of 50 slides, it was a rather good index of prognosis. It was less accurate in the series of 136 patients treated radiologically and the 103 patients

TABLE IX.—THE RELATION OF AGE, BASAL CELLS, AND 5 YEAR SURVIVAL IN PATIENTS TREATED RADIOLOGICALLY

Stage	9 per cent or less basal cells				10 per cent or more basal cells			
	Age, 50 years or less		Age, 51 years or more		Age, 50 years or less		Age, 51 years or more	
	No.	Cures	No.	Cures	No.	Cures	No.	Cures
I	3	0	12	5	8	5	12	3
II	20	6	9	3	16	10	20	13
III	10	1	4	1	3	1	11	4
IV	2	0	2	0	0	0	4	0
All	35	7 (20%)	27	9 (33%)	27	16 (59%)	47	20 (43%)
II, III, IV*	32	7 (22%)	15	4 (27%)	19	11 (58%)	35	17 (49%)

*Stage I cases are excluded from the total in this line in order to evaluate better the distribtion of patients by age, because many of the younger in the stage I group were treated surgically.

treated surgically. Although basal cell incidence lacked the precision of SR in prognosis, it showed the same general trend as SR in both series, thus supporting the different outlook depending upon the mode of treatment. Basal cell counts divide the patients into sufficiently different categories to be of some value in the management of the case. For example, stage II lesions, in the presence of many basal cells, are better treated radiologically with its 64 per cent salvage rate than surgically, where only 1 of 10 patients survived. By contrast, if basal cells are lacking, the outcome after surgery is better than after radiation—63 per cent as against 31 per cent.

In the irradiated series of 136 patients, 54 per cent had many basal cells and only 37 per cent had marked SR. Two-thirds of 74 patients with many basal cells had marked SR and only 2 of the 62 patients with few basal cells had marked SR. Only 2 of the 51 patients with marked SR had few basal cells. Thus one may conclude that the patient must have numerous basal cells if she is to hope to have marked SR, but that basal cells alone are of modest advantage. Marked SR is rarely found in the absence of many basal cells.

The real significance of basal cells in patients with cancer of the cervix lies not in its prognostic value, but rather in the understanding of the host-tumor relationship. This is a subject that cannot be satisfactorily dealt with here, partly because so much is pure speculation. However, the following hypothesis is suggested: the host reaction to the tumor is at two levels; one, a systemic mobilization in which there is a relative androgen preponderance manifested in a high proportion of basal cells; the other, which may be either a generalized or a local phenomenon, is regarded as a superimposed resistance indicated by numerous SR cells.

It is concluded that SR is a useful prognostic index in patients with cancer of the cervix and

TABLE X.—THE RELATION BETWEEN SR, BASAL CELLS, AND 5 YEAR SURVIVAL IN PATIENTS TREATED RADIOLOGICALLY

Stage	10 per cent or more SR 10 per cent or more basal cells		10 per cent or more SR 9 per cent or less basal cells		9 per cent or less SR 10 per cent or more basal cells		9 per cent or less SR 9 per cent or less basal cells	
	No.	Cures	No.	Cures	No.	Cures	No.	Cures
I	12	7	0	0	8	1	15	5
II	29	23	1	1	7	0	28	8
III	7	5	1	1	7	0	13	1
IV	1	0	0	0	3	0	4	0
All	49	35 (71%)	2	2	25	1 (4%)	60	14 (23%)

that it may serve in the selection of the appropriate form of treatment. The estimation of SR is a technique that can be taught and learned in a reasonable period of time. The proportion of basal cells is of limited prognostic value but follows the same general trend as SR.

SUMMARY

Vaginal smears, taken from patients with a stage I or II cancer of the cervix before treatment, have been evaluated. A marked sensitization response and, to a less extent, many basal cells indicate a favorable prognosis when treated radiologically and a poor prognosis when treated surgically. The opposite is found in those with poor SR, for the salvage rate is significantly better in the surgical group than in the radiologic group. Series of 136 patients treated radiologically and 103 patients treated surgically are presented.

Evaluation of the same set of 50 vaginal smears by 10 different observers indicates a high degree of reproducibility in both SR and basal cell appraisal.

It is concluded that SR is a useful prognostic index and that it can be learned fairly readily.

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A CLINICAL STUDY OF TWO HUNDRED ONE CASES OF REGIONAL (SEGMENTAL) COLITIS

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REGIONAL (segmental) colitis may be defined as an inflammatory disease of unknown etiology involving initially one or more segments of the large intestine, exclusive of the rectum and rectosigmoid, either as a continuous lesion or as multiple discontinuous lesions.

One of us (Bargen) and Weber, in 1930, reported 23 cases of this disease and used the term "regional migratory chronic ulcerative colitis." Crohn and Berg, in 1938, reported their study of 17 similar cases and used the term "right-sided (regional) colitis" according to their observation that the disease began in the right side of the colon. Barbosa, one of us (Bargen), and Dixon published a report in 1945 on a study of 140 cases of "regional segmental colitis." This was followed in 1947 by the report of Crohn and associates (7) concerning 77 cases. Since 1947 no large series of such cases has been reported but a number of case reports have appeared in the medical literature from this continent and from abroad, among them those of Brownlee, Epstein and associates, Kertzner, and Thompson.

Comparatively little, then, has been written about this disease. Furthermore, controversy exists as to whether medical or surgical treatment gives the better result; in connection with surgical treatment, opinion varies as to whether short-circuiting or resective operation is the procedure of choice.

This study was undertaken, therefore, to describe the clinical features of the disease, to compare the results of medical and surgical treatment and to determine, if possible, which of the surgical procedures just mentioned is the one of choice.

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Abridgment of portion of thesis submitted by Dr. Neuman to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

MATERIAL

The material for this study consisted of the records in all cases of regional (segmental) colitis seen at the Mayo Clinic during the years 1924 to 1950, inclusive. The diagnosis was established by examination of stools, proctosigmoidoscopy, roentgenograms of the colon after a barium enema, and, in selected cases, by roentgenologic examination of the small intestine. The following types of cases were excluded from the study: (1) those in which any pathologic change in the terminal portion of the ileum could not be attributed, with reasonable certainty, to retrograde involvement secondary to the main colonic lesion; (2) those in which, on first examination at the clinic, there was any abnormality of the rectum and rectosigmoid, however slight, that could not be definitely attributed to the perirectal and perianal complications of the disease; (3) those in which definitive operations had been done elsewhere for the disease prior to the first examination at the clinic; and (4) those in which 2 concomitant lesions were present, 1 in the large intestine and 1 in the small intestine, separated by a normal segment of intestine. A total of 201 cases satisfied these criteria.

CLINICAL FINDINGS

Race, sex, and age at onset. The 201 patients included a wide variety of racial origins; no Orientals were encountered. Forty-seven (23.4 per cent) were Jewish. One patient was a Negro. One hundred and six patients were females and 95 were males, a ratio of 1.11 to 1. The mean age of the patients at the onset of symptoms was 29.1 years for males and 28.5 years for females. The highest incidence of the disease occurred in the third, fourth, and second decades of life in that order; all decades up to and including the seventh were repre-

TABLE I.—AGE AT ONSET OF SYMPTOMS AND SEX INCIDENCE OF REGIONAL COLITIS IN 201 CASES

Age at onset, years	Males		Females		Total	
	No.	Per cent	No.	Per cent	No.	Per cent
0–9	1	1.1	0	0.0	1	0.5
10–19	20	22.2	16	15.6	36	18.7
20–29	33	36.7	40	38.8	73	37.8
30–39	17	18.9	25	24.3	42	21.8
40–49	11	12.2	13	12.6	24	12.4
50–59	6	6.7	7	6.8	13	6.7
60–69	2	2.2	2	1.9	4	2.1
Total	90*	100.0	103*	100.0	193	100.0
Mean age	29.1		28.5		28.8	

*Age at onset indeterminate in 5 males and 3 females.

sented. No significant sex preponderance according to decades was noted (Table I).

History. Nothing of significance was elicited from the family history or past history of these patients. The majority of patients gave no history of significant factors at onset. However, 28 patients dated the onset of their disease to some particular illness, surgical operation, or physical or mental trauma. Fourteen of these 28 patients stated that their symptoms began immediately or soon after a surgical operation as follows: in 8 after operation for perianal or perirectal abscess or fistula, in 3 after hemorrhoidectomy, and in 3 after appendectomy. Eight patients dated their first symptoms to a particular illness or infection as follows: 5 to an infection of the upper part of the respiratory tract described as "flu" or influenza, 1 to scarlet fever, 1 to a streptococcal sore throat, and 1 to epidemic diarrhea. Three patients dated the onset of their disease to severe abdominal trauma. In 1 patient the symptoms began after parturition; 1 patient dated the onset of her disease to the first trimester of her first pregnancy; and in 1 patient the symptoms began after an emotional disturbance brought on by the death of a near relative.

TABLE II.—SYMPTOMS IN REGIONAL COLITIS

Symptoms	Patients	Per cent
Diarrhea	174	86.5
Bloody stools	98	48.7
No blood in stools	76	37.8
Weight loss	146	72.6
Abdominal pain	138	68.6
Fever	80	39.8
Generalized weakness	65	32.3
Constipation	21	10.4
Anorexia	21	10.4
Nausea and vomiting	20	9.9
Rectal discharge (mucous or purulent)	19	9.4
Blood in stools without diarrhea	11	5.4
Rectal pain	9	4.4
Abdominal distention	7	3.4
Intestinal hemorrhage	6	2.9
Menstrual abnormalities	5	2.4
Arthritis	5	2.4
Alternating constipation and diarrhea	4	1.9
Fecal fistula in abdominal wall	4	1.9
Excessive flatus	4	1.9
Rectal tenesmus	3	1.4
Dermatitis	3	1.4
Rectovaginal fistula	2	1.0

Mode of onset, duration, and course of disease prior to first examination at the clinic.—The average duration of symptoms prior to the first examination at the clinic was 3.6 years. The onset was classed as sudden in 122 (62.2 per cent) of 196 patients, gradual in 66 (33.7 per cent), and insidious in 8 (4.1 per cent). In 5 patients the mode of onset was not recorded.

The subsequent course was intermittent in 127 (63.2 per cent) of the 201 patients, and continuous in 66 (32.8 per cent). In the remaining patients both the onset (as already indicated) and the subsequent course of the disease were classed as insidious. Of these 8 patients, 4 complained only of constipation of many years' duration, with recent increased effectiveness of laxatives in 2; the respective single complaints in the remaining 4 patients were weakness, rectovaginal fistula after surgical drainage of a perirectal abscess, fatigue and mild dyspepsia, and exertional precordial pain.

Forty-seven (23.4 per cent) of the 201 patients had operations after onset of the disease and prior to the first visit to the clinic. Of these, 31 had surgical treatment for perirectal and perianal abscesses and fistulas, 7 had hemorrhoidectomy alone, 4 had combined fistulectomy and hemorrhoidectomy, 4 had appendectomy, and 1 had surgical drainage of an intra-abdominal abscess.

Periods of reactivation and exacerbation were characteristic of the clinical course of the disease. Exciting or precipitating causes were

not elicited in the majority of instances. Fifteen patients, however, related reactivations and exacerbations to infection of the upper part of the respiratory tract, 7 to operations undertaken for perirectal and perianal conditions, 3 to emotional upsets, 3 to dietary indiscretion, 2 to physical exhaustion, 1 to pregnancy, 1 to marriage, 1 to an automobile accident, and 1 to infection of the urinary tract.

Symptomatology. The symptoms included those which were manifestations of intestinal disease and those which were of systemic or constitutional origin. The various symptoms of both groups and their relative frequency of occurrence are shown in Table II. Of the 201 patients, 174 experienced diarrhea at some time during the course of their disease; it constituted the chief complaint in 149 patients. The number of stools per 24 hours was as follows: 3 to 5 in 80 patients (45.9 per cent), 6 to 8 in 47 patients (27.1 per cent), 9 to 11 in 29 patients (16.7 per cent), 12 to 15 in 15 patients (8.6 per cent), and 16 or more in 3 patients (1.7 per cent). Approximately half of the patients had noted gross blood in their stools. Approximately two-thirds of the patients complained of cramplike abdominal pain, moderate to marked in severity and relieved partially or completely by bowel movement. Intermittent fever occurred in more than a third of the patients; the increase in temperature frequently occurred late in the afternoon and was usually slight, varying from 1 to 2 degrees F. above normal. Twenty-one patients complained of constipation; in all but 1 of these, constipation had been present for many years, and 4 gave a history of consumption of excessive amounts of laxatives for long periods. Eleven patients had noted blood in their stools without diarrhea. Frank intestinal hemorrhage had occurred in 6 additional patients; in 1 of these it was massive, requiring multiple transfusions.

Physical examination. Results of physical examination were entirely negative in 120 patients. Loss of weight was evident in 69 patients and 18 of these showed pronounced malnutrition. Pallor of the skin and mucous membranes was noted in 60 patients. Abdominal tenderness was present in 55 patients and was usually located in the right or left lower quadrant. Other findings included a mass in the right lower quadrant of the abdomen in 3 patients, a mass in the left lower quadrant in 2, and fecal fistulas in the abdominal wall in 4. The fistulas in 2 of these cases had occurred after appendectomy and in 2 after incision and drainage of intra-abdominal abscesses.

Proctosigmoidoscopic examination. Results of this examination were within normal limits in 173 patients. Perirectal and perianal suppurative conditions were observed in 27 patients; a rectovaginal fistula was present in 2

TABLE III.—LOCAL (INTESTINAL) COMPLICATIONS IN REGIONAL COLITIS

Complications		Patients	Per cent
Polypoid hyperplasia of colonic mucosa		64	31.8
Perirectal and perianal involvement		45	22.3
Intestinal hemorrhage		17	8.4
Localized stricture		14	6.9
Rectum	5		
Descending colon	3		
Sigmoid	2		
Hepatic flexure	2		
Ascending colon	1		
Transverse colon	1		
Perforation		13	6.4
Cecum	3		
Descending colon	3		
Sigmoid	3		
Ascending colon	1		
Splenic flexure	1		
Rectum	1		
Site undetermined	1		
Fistula		13	6.4
Rectovaginal	6		
Colocutaneous	5		
Internal	2		

TABLE IV.—DISTANT (SYSTEMIC) COMPLICATIONS IN REGIONAL COLITIS

Complications		Patients	Per cent
Arthritis		31	15.4
Cutaneous lesions		17	8.4
Pyoderma gangraenosum	7		
Erythema nodosum	7		
Pustular dermatitis	1		
Acne cachecticorum	1		
Nonspecific dermatitis	1		
Menstrual abnormalities		13	6.4
Ocular complications		6	2.9
Iridocyclitis	5		
Chorioretinitis	1		
Severe deficiency states		6	2.9
Infection of urinary tract		5	2.4
Stomatitis		5	2.4
Mental aberrations		2	1.0
Retarded growth and development		2	1.0
Severe renal insufficiency		1	0.5
Intrahepatic abscess		1	0.5

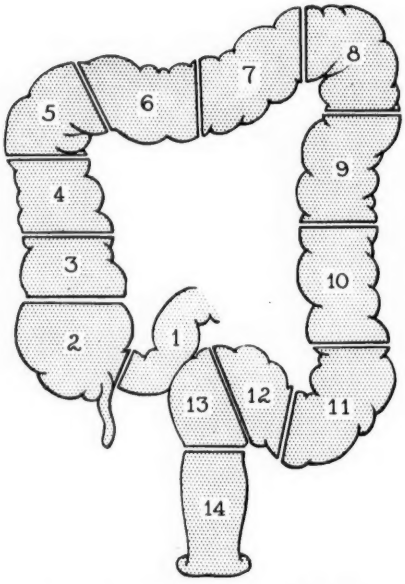

Fig. 1. Segmental divisions of the colon.

of these. In 1 patient the lower limit of the lesion was seen.

Laboratory data. Many patients exhibited slight to moderate anemia of the hypochromic microcytic type. Eosinophilia and toxic neutrophils in the peripheral blood were noted fairly frequently. The total leucocyte count was normal or only slightly increased even during active phases of the disease. The sedimentation rate of the erythrocytes was consistently increased during recurrences and exacerbations of the disease. Examination of stools revealed numerous pus cells in 91 patients. Of the 76 patients who never had noted gross blood in their stools, 31 showed large numbers of erythrocytes in their stools.

Location of the lesion. To indicate the site and extent of involvement on first examination at the clinic, the colon was divided into segments numbered *2* to *14* (Fig. 1). The terminal portion of the ileum was numbered *1*. The site and extent of involvement were determined by roentgenologic examination alone in those patients treated medically and by this in addition to operative findings in those who had short-circuiting or resective operations.

In 30 patients (14.9 per cent), the lesion was confined to the right half of the colon (segments *2* to *6* inclusive), involving all or segments of it in continuity. In 25 patients (12.4 per cent), the lesion was confined to the left half of the colon (segments *7* to *12* inclusive). In 131 patients (65.2 per cent), the lesion involved segments of the right and left halves of the colon in continuity. In 15 patients (7.5 per cent), the lesion involved segments of the right and left halves of the colon discontinuously (involvement of skip areas). The terminal portion of the ileum was involved in a total of 45 patients (22.4 per cent).

Figure 2 illustrates the number of times each segment of the colon was involved. The segments of the transverse colon were involved most frequently, and the segments of the right half of the colon were involved somewhat more frequently than those of the left half. Progressive decrease was noted in the frequency of involvement of the various segments beginning in the proximal half of the transverse colon and progressing toward the rectum.

Complications. The complications of the disease were divided into two groups, namely, local (intestinal) and distant (systemic); they include complications present on admission and those developing subsequently. The local, or intestinal, complications are listed in Table III. The most frequent intestinal complication was inflammatory polypoid hyperplasia of the colonic mucosa.

Perirectal and perianal suppurative manifestations constituted the second most frequent intestinal complication and included abscesses, fistulas, and sinuses.

Frank intestinal hemorrhage occurred in 17 patients; in 7 of these the hemorrhage was massive, requiring transfusion, and in 1 patient massive hemorrhage resulted in death.

Formation of localized strictures was observed in various parts of the colon in 14 patients; the most frequent site of this complication was the rectum. In 4 patients, rectal stricture followed extension of the disease to involve the rectum; in 1 patient, rectal stricture resulted from extensive perirectal abscesses. Symptoms of intestinal obstruction occurred in only 1 patient.

Perforation, noted in 13 patients, was usually chronic in nature, resulting in formation of localized abscesses. However, generalized peritonitis developed in 1 patient, resulting in death.

Fistulas formed in 13 patients. Of the 5 colocutaneous fistulas, 3 appeared spontaneously after perforation and formation of abscesses and 2 occurred after surgical drainage of an abscess. Internal fistulas occurred in only 2 patients and were located between the terminal portion of the ileum and the hepatic flexure and between the cecum and the sigmoid respectively.

The distant, or systemic, complications are listed in Table IV.

TREATMENT

Of the 201 patients included in this study, 10 received no treatment at the clinic, 150 received medical treatment, 16 had some type of short-circuiting operation, and 25 had resection of the lesion and re-establishment of intestinal continuity in one or more stages.

Follow-up information was not available in 5 of the 10 patients who received no treatment; in the remaining 5 patients, there was follow-up by letter only. Two of these 5 patients had received no subsequent medical or surgical treatment at any time and stated that they were in excellent health 9 years after their first and only visit to the clinic; 1 had received medical treatment elsewhere and had died of colitis 2 years later; 2 had undergone short-circuiting operations (ileosigmoidostomy) within 1 year.

RESULTS OF MEDICAL TREATMENT

Briefly, medical treatment consisted of adequate rest, a diet high in protein and vitamins and low in residue, various supportive measures, such as vitamins given parenterally, blood transfusions, and intravenous infusions, and the administration of sedatives and antispasmodics. In addition, some patients received some of the less soluble sulfonamide compounds or various antibiotics.

Of the 150 patients who received medical treatment at the clinic, follow-up information, by either letter or repeat visit, was not available in 27. Follow-up information by letter only was available in 24 patients. Of these, 1 patient reported no subsequent symptoms 2.2 years later. Three patients reported subsequent symptoms but no further treatment and described their general health as good 1.6, 3.3, and 11 years later, respectively. In another 7 patients, subsequent information was obtained by letter at an average period of 4.03 years after dismissal from the clinic and all 7 had experienced subsequent symptoms requiring medical treatment; 2 of the 7 had died, presumably of the disease, 2 reported their general health as good, and 3 reported their general health as fair. Thirteen patients had noted subsequent symptoms requiring combined medical and surgical treatment or surgical treatment alone; of these, 5 had undergone short-circuiting procedures, 2 had undergone ileostomy, 4 had undergone resective procedures, and 2 had subsequent operations of undetermined nature and extent.

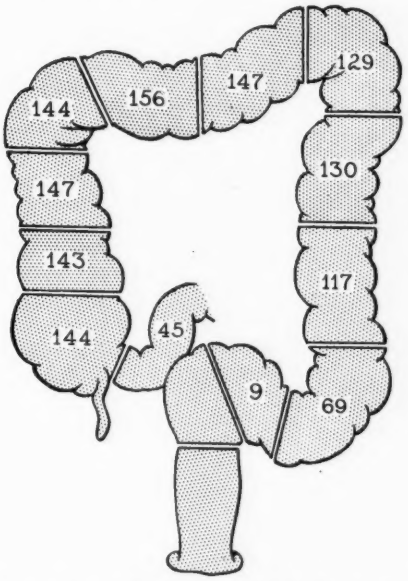

Fig. 2. Segmental incidence of colonic involvement in 201 cases of regional colitis.

Follow-up information by repeat visits and by letter was available in 99 patients. Appraisal of the data revealed no significant dif-

TABLE V. — GRADE OF SEVERITY OF RECURRENCES IN REGIONAL COLITIS

Recurrence	Severity, grade	Patients	Per cent
First	1	41	66.1
	2	9	14.5
	3	12	19.4
Total		62	100.0
Second	1	15	53.6
	2	7	25.0
	3	6	21.4
Total		28	100.0
Third	1	8	53.3
	2	4	26.7
	3	3	20.0
Total		15	100.0

ference in results between those patients receiving and those not receiving antibiotics. No distinction was made, therefore, between the two groups of patients. Of these 99 patients, 4 (4.1 per cent) showed little or no response to medical treatment for adequate periods. Two of these patients died elsewhere of colitis within 2 months of leaving the clinic, 1 underwent partial colectomy elsewhere 4 months later, and 1 experienced continuation of symptoms for a known period of 18 months.

In 33 patients (33.3 per cent), no recurrences took place throughout an average follow-up period of 6.7 years. In 34 patients (34.3 per cent), single recurrences only occurred throughout an average follow-up period of 4.1 years. By recurrence is meant return of symptoms with or without extension of the disease to involve additional segments of the colon as manifested roentgenologically. In 28 patients (28.3 per cent), 2 or more recurrences were noted throughout an average follow-up period of 7.9 years.

In all, 62 patients (62.6 per cent) experienced recurrences, whether single or multiple, throughout the follow-up period. Two-thirds of these patients had the first recurrence within 2 years of medical treatment on their initial visit to the clinic; the majority of these recurrences appeared within the first year. The remaining third had the first recurrence from 3 to 10 years later. In those patients who had multiple recurrences, the second recurrence came within 2 years of the first in 70 per cent of cases, the majority again occurring within the first year.

Severity of recurrences. Recurrences were divided into three grades according to severity. A return of symptoms without extension of the disease was classed as a grade 1 recurrence. A return of symptoms with extension of the disease to previously uninvolved segments of the colon constituted a recurrence of grade 2 severity. Progression of the disease to involve the rectosigmoid and rectum constituted a recurrence of grade 3 severity. Recurrences were classified according to grade of severity and the relative frequency of each grade was calculated. These calculations were extended to the third recurrence to see if progressive increase in severity took place with each successive recurrence (Table V). No significant difference was noted.

Twenty recurrences were of grade 2 severity. The direction of extension of the lesion in these instances was proximal (toward the terminal portion of the ileum) in 6, distal (toward the rectum) in 8, and both proximal and distal in 6. Recurrences of grade 3 severity numbered 21; in addition to extension of the lesion distally to involve the rectosigmoid and rectum, extension toward the terminal portion of the ileum was also present in 6 cases.

RESULTS OF SURGICAL TREATMENT

Complications and operative mortality. Of the 16 patients subjected to short-circuiting procedures, 1 had a colocutaneous fistula after operation. Two patients, both operated on before the advent of preoperative intestinal chemotherapy, died of generalized peritonitis 12 and 23 days respectively after operation.

Of the 25 patients treated by resection of the lesion and re-establishment of intestinal continuity in one or more stages, 7 experienced immediate postoperative complications, namely intra-abdominal abscesses requiring incision and drainage in 3, fecal fistulas in the abdominal wall in 2, intraperitoneal hemorrhage in 1, and bronchopneumonia and atelectasis in 1. One patient died 3 weeks after operation of generalized peritonitis. Three patients died elsewhere within 6 months

of postoperative dismissal from the clinic; 1 of these died of intestinal obstruction caused by volvulus of the ileum, 1 of obstruction of the small intestine and generalized peritonitis, and 1 of generalized peritonitis as the result of an intra-abdominal abscess.

Recurrences after short-circuiting procedures. As stated previously, 2 patients died in the immediate postoperative period; follow-up information was not available in 3 patients. Of the remaining 11 patients, 6 had no recurrences throughout an average follow-up period of 6.4 years. Single recurrences only occurred in 3 patients throughout an average follow-up period of 3.4 years; in 2 patients, multiple recurrences took place throughout follow-up periods of 1.1 and 12.1 years respectively.

Recurrences after resective procedures. As already indicated, 1 patient died in the immediate postoperative period and 3 patients died within 6 months of operation. Follow-up information was not available in an additional 3 patients. Of the remaining 18 patients, 10 had no recurrence throughout an average follow-up period of 3.4 years. Single recurrences only occurred in 6 patients throughout an average follow-up period of 3.3 years; in 2 patients, multiple recurrences took place throughout follow-up periods of 5.2 and 7.1 years respectively.

Comparative results of medical and surgical treatment. Recurrences after medical and surgical treatment are compared in Table VI. No differentiation is made in this table between short-circuiting and resective procedures.

TABLE VI. — COMPARATIVE RESULTS OF MEDICAL (99 PATIENTS) AND SURGICAL (35 PATIENTS) TREATMENT

Treatment							
Medical				Surgical			
Recurrences	Patients	Per cent	Average follow-up, yr.	Recurrences	Patients	Per cent	Average follow-up, yr.
None	33	33.3	6.75	None	16	45.7	4.90
Single	34	34.3	4.10	Single	9	25.7	3.35
Multiple	28	28.3	7.90	Multiple	4	11.4	6.35
Total	95*			Total	29†		

*Four patients showed no response to medical treatment.
†Three patients died in the immediate postoperative period and 3 died within 6 months of operation.

COMMENT

It has been estimated that regional (segmental) colitis constitutes 4 to 10 per cent of all cases of chronic ulcerative colitis. As already indicated, the cause is unknown; all investigative work, including pathologic study of the lesions, has given no information as to a specific etiologic agent or agents. It is a disease of young people, having its greatest incidence in the third decade of life. The incidence is approximately the same for both sexes. While no racial predilection has been mentioned in the literature, this study indicates a definite predilection for members of the Jewish race. The literature contains only a rare mention of the disease occurring in Negroes; in this study, only 1 patient was a Negro.

Initially, any segment or segments of the colon may be involved exclusive of the rectum and rectosigmoid. Segments of the right half of the colon are more frequently involved than the left, although in this study the greater frequency of involvement of the segments of the right half of the colon as compared with the left was not significant. Furthermore, in 12 per cent of the patients in this study, the lesion was confined to the left half of the colon. The term "right-sided regional colitis" would appear, therefore, to be somewhat inaccurate and misleading.

The disease may extend in either direction from the initial site of colonic disease. Involvement of the terminal portion of the ileum secondary to the main colonic lesion occurs frequently, having been reported in 40 per cent of the 77 cases reported by Crohn and associates (7) and in 25 per cent of the 140 cases reported by Barbosa and co-workers. In the present study, the terminal portion of the ileum was involved in 22 per cent of patients. Spread of the disease is thought to occur by direct extension taking place mainly in the mucosa and submucosa. Garlock expressed the opinion that spread occurs by the subserosal and mesenteric lymphatic vessels as well. Our study confirms previous observa-

tions that extension of the pathologic process is more rapid toward the rectum than toward the ileum. It has been stated that the flexures of the colon, particularly the hepatic and sigmoid flexures, constitute barriers or at least points of delay in the further progression of the disease. The present study offered no evidence of such effect.

The high incidence of perirectal and perianal suppurative complications in this study is in agreement with the incidence reported by others. While inflammatory polypoid hyperplasia of the mucosa of the involved segment of intestine is extremely common, malignant change, if it occurs at all, is rare. Gross hemorrhage from the intestine is a more frequent and more severe complication than was previously recognized.

Although complete remission of symptoms and even disappearance of the objective signs of the disease have been noted after medical treatment by Barbosa and associates, by one of us (2) and by Bockus, medical management on the whole has been disappointing and the incidence of recurrence great. For this reason, surgical treatment has been considered at times to be the treatment of choice. The literature contains a number of reports of good results obtained by excision of the lesion, although the follow-up period has been short in most instances; Barbosa and his associates stated that the incidence of recurrence after resection and anastomosis is minimal. While this study confirms the high incidence of recurrence after medical treatment, it indicates a greater incidence of recurrence after surgical treatment than has been reported previously, probably because of the greater length of our follow-up periods. The data obtained, however, appear to indicate a significantly lower incidence of recurrence after surgical treatment than following medical treatment. It appears inadvisable to make any more definite statement in regard to the relative efficacy of medical and surgical treatment, since the number of patients treated medically was approximately three times the number treated surgically. Furthermore, the length of follow-up period in medically treated patients averaged 1.4 years longer than that of the surgically treated patients.

Crohn and co-workers (7) stated that recurrences after surgical resection or short-circuiting procedures invariably occur in the more distant parts of the sigmoid and rectum and not in the ileum. In this study, involvement of the ileum above the anastomosis did occur after resection but not after short-circuiting operations.

The incidence of recurrence has been reported to be greater after short-circuiting procedures than after resection. The disparity in this study between the number of patients treated by short-circuiting operations and the number treated by resection allows no definite conclusions in regard to the relative efficacy of each procedure. However, evaluation of the data suggests that the number of patients who experience recurrences after short-circuiting operations is not significantly greater than that after resection for the same length of follow-up. The data further suggest that the first recurrrence after resection is much more likely to result in extension of the lesion to the rectosigmoid and rectum than is the first recurrence after short-circuiting operations.

SUMMARY AND CONCLUSIONS

A study has been made of the records in 201 cases of regional (segmental) colitis seen at the Mayo Clinic from 1924 to 1950, inclusive.

The greatest incidence of the disease occurred in the third decade of life. Approximately 25 per cent of patients in this study were members of the Jewish race. No significant difference in sex incidence was noted.

The most frequent symptoms were diarrhea, loss of weight, abdominal pain, and fever. The most common findings on physical examination were evidence of loss of weight, pallor of the skin and mucous membranes, and abdominal tenderness. Proctosigmoidoscopic examination revealed perirectal and perianal complications in 13.4 per cent of patients on initial examination at the clinic. The most frequent laboratory finding was anemia of the hypochromic microcytic type. In two-thirds of the patients, the lesion involved segments of both right and left halves of the colon in continuity. In the remaining third, the lesion was confined to either the right or left half of the colon or involved both

halves discontinuously. Malignant change in the colon was not encountered.

The results after medical and surgical treatment have been presented and compared. The incidence of postoperative complications was considerably greater after resective procedures than after short-circuiting operations. Two patients subjected to short-circuiting operations and 1 patient subjected to resection died in the immediate postoperative period, giving an operative mortality of 7.3 per cent.

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THE PATHOLOGY OF REGIONAL (SEGMENTAL) COLITIS

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IN 1930 Bargen and Weber described a form of ulcerative colitis in which there was no proctosigmoidoscopic evidence of disease in the rectum and rectosigmoid segments but in which segments of the more proximal parts of the colon were shown by radiologic examination to be involved. They described this condition under the term "regional migratory chronic ulcerative colitis." In 1938, Crohn and Berg described a similar condition under the name "right-sided regional colitis" according to their observation that the disease began in the right side of the colon and progressed to the left.

Reports of localized ulcerative disease of the colon similar to the condition described by Bargen and Weber and by Crohn and Berg have appeared in the medical literature since the beginning of the century. Prior to 1907, cases of hyperplastic tuberculosis of the large intestine had been described in which no caseation or tubercle bacilli could be demonstrated on pathologic examination of the lesion but in which tubercle formations including giant cells were observed. In 1907, Moynihan described nonspecific inflammatory lesions of the large intestine, unassociated with diverticula, which simulated malignant lesions. In 1908, Robson described inflammatory lesions of the large intestine simulating malignant lesions and postulated that the pathologic process was a "chronic infiltrating colitis." In 1913, Dalziel described 4 cases of what he termed "chronic interstitial enteritis"; in 1 of these the disease involved the sigmoid flexure and in another the transverse colon. He presented gross and microscopic descriptions of the resected specimens, concluded that the disease was not of tuberculous nature, and stated that resection of these lesions was followed by complete restoration of health.

Läwen in 1914, in his paper on fibroblastic appendicitis, referred to inflammatory tumors of the cecum and adjacent ascending colon not having their origin in the appendix. He mentioned the possibility of confusing these lesions with hyperplastic intestinal tuberculosis. Tietze in 1920 included similar lesions in a comprehensive article on inflammatory intestinal masses. In 1923, Moschcowitz and Wilensky described 4 cases of nonspecific granulomas of the intestine, in 3 of which the lesions were confined to segments of the colon other than the rectum and rectosigmoid segments. They emphasized the granulomatous nature of the lesion and commented on its resemblance to hyperplastic tuberculosis. During the period from 1931 to 1937, a number of case reports of localized ulcerative disease of the proximal colon appeared in the medical literature under such terms as "regional chronic ulcerative colitis," "chronic regional colitis," and "regional colitis." In 1945, Barbosa, Bargen, and Dixon published a report, under the title "regional segmental colitis," on their study of 140 cases of ulcerative colitis involving segments of the colon other than the rectum and rectosigmoid segments.

The term "regional (segmental) colitis," then, refers to an inflammatory disease of unknown origin involving one or more segments of the large intestine. The rectum and rectosigmoid segments must be free of involvement at the time of the first examination. The lesion may extend in either direction from the initial site of colonic involvement, although the major extension is toward the rectum. Involvement of the terminal ileum secondary to the main colonic lesion occurs quite frequently, having been reported in 40 per cent of Crohn, Garlock, and Yarnis's series of 77 cases and in 25 per cent of 140 cases reported by Barbosa, Bargen, and Dixon.

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Abridgment of portion of thesis submitted by Dr. Neuman to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

The pathologic features of this disease, as described later, are based on gross and microscopic observations on 25 specimens removed surgically in the treatment of this disease.

MATERIALS AND METHODS

Following resection of the involved segment of intestine, all of the specimens had been preserved in 10 per cent formalin for permanent museum storage. All of these specimens were available, and all were satisfactory for study. The gross characteristics of the lesions were noted and tabulated on separate filing cards. Multiple blocks of tissue were cut from the involved segment of intestine and, wherever possible, from areas of grossly normal intestine at 3 and 6 centimeter levels proximal and distal to the gross confines of the lesion. In addition, blocks were taken from lymph nodes located in the mesentery of the involved segment. A total of 300 blocks were cut, an average of 12 per specimen. These blocks were placed in fresh 10 per cent formalin solution, sectioned with a freezing microtome, stained with hematoxylin and eosin, and mounted permanently on glass slides. The sections of intestinal wall were examined layer by layer, all data being recorded on individual filing cards.

The single microscopic criterion used to exclude intestinal tuberculosis was the absence of caseation.

PATHOLOGY

Gross features of the colonic lesion. The length of colon involved varied greatly. Longitudinal shortening of the segment involved was a consistent gross feature; in many cases there was circumferential constriction also, but in a few specimens the circumference of the wall of the colon appeared normal and in 1 specimen there was moderate dilatation of the involved segment. Excessive amounts of mesenteric fat appeared to surround the diseased portion of colon, whereas normally such fat is confined for the most part to the posterior zone of attachment.

Thickening of the wall of the colon was consistently noted. The thickness of the colonic wall in a group of "normal" controls was from 5 to 6 millimeters as measured through the taeniae and 3 to 4 millimeters elsewhere. In regional colitis all degrees of thickening were manifested in the same specimen. In 7 specimens the thickness of the colonic wall in the involved area varied from 12 to 15 millimeters, in 4 from 9 to 11 millimeters, and in 10 from 7 to 8 millimeters. In the remaining 4 specimens the thickness of the colonic wall was within normal limits. Almost invariably, the greater the thickening of the wall, the narrower was the size of the lumen of the involved segment. In 8 specimens the diameter of the lumen was reduced to approximately 1 centimeter.

Fig. 1. Section through the entire thickness of the wall of the colon. Note the shallow mucosal ulceration and, in addition, one area of ulceration extending to the subserosa. Hematoxylin and eosin, ×6.

Ulceration of the mucous membrane was apparent grossly in 17 of the 25 specimens. In most cases the ulcerative process was

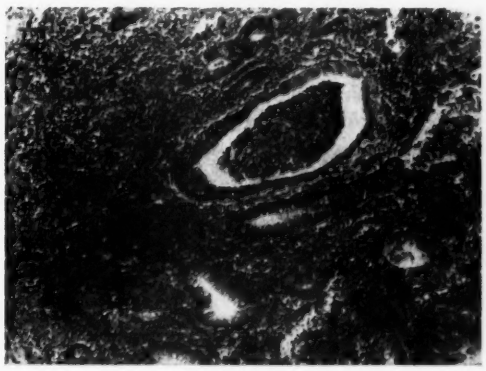
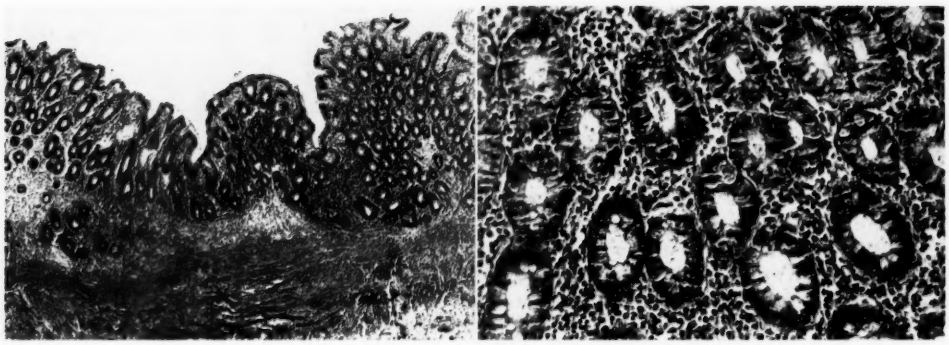


Fig. 2. Section through the wall of the colon showing purulent cryptitis. Hematoxylin and eosin, ×74.



a b

Fig. 3. a, Inflammatory polypoid hyperplasia of the colonic mucosa. Hematoxylin and eosin, ×22. b, Higher magnification of an area of the mucosa shown in a. Hematoxylin and eosin, ×148.

present diffusely throughout the involved segment, but occasionally it was segmental in distribution with intervening zones of atrophic or hypertrophic-appearing mucous membrane. The size of the individual ulcers varied from several millimeters to several centimeters. Usually they were shallow with little or no undermining of the edges. The ulcers were linear and ovoid in configuration. In 12 specimens linear and ovoid ulcerations were present around the entire circumference of the wall; in 2 of these, ulceration appeared most marked along the line of mesenteric attachment. In 5 specimens the ulcerations were located only along the line of mesenteric attachment. The intervening mucosa was smooth and thin with complete loss of transverse folds in some areas, while in others it was hypertrophic. Polypoid hyperplasia was noted in 14 of the 25 specimens. The polyps varied considerably in size and were usually numerous. In several of the specimens the entire mucosal surface was converted into myriads of pedunculated polyps.

A striking feature was the sharp and rapid change from involved to normal-appearing intestine. Within an area of 1 to 2 centimeters mucosal ulceration and mural thickening gave way to normal mucosa and wall of normal thickness.

In only 2 cases were the mesenteric regional lymph nodes obviously enlarged.

Microscopic features of the colonic lesion. Ulceration of the mucous membrane was observed in 20 specimens. In 6 of these the zone of tissue loss was confined to the mucosa; in 13 it extended for variable distances into the submucosa but not into the muscularis propria; in 1 specimen ulceration extended into the subserosa (Fig. 1). The ulcer bases were surrounded by broad or narrow zones of acute and subacute inflammatory cells extending more deeply into the wall. Beneath these zones were areas of granulation tissue heavily infiltrated with subacute and chronic inflammatory cellular elements or, in a few cases, zones of rather dense fibrous tissue with comparatively little cellular infiltration. In 3 specimens abscesses were seen in the mucosa and submucosa adjacent to areas of ulceration. Occasionally areas of hemorrhage were seen at the ulcer bases. In 1 specimen only, giant cells and granuloma formation were observed immediately adjacent to areas of ulceration. Specific changes in relation to the various coats of the bowel wall were as follows:

The mucous membrane proper.—In addition to ulceration, a consistent feature was the presence of edema and diffuse inflammatory cell infiltration. The cells consisted largely of plasma cells and epithelioid cells, with varying numbers of polymorphonuclear leucocytes. As a rule, polymorphonuclear leucocytes were not numerous except near areas of ulceration. In 6 specimens, however, widely scattered crypts were observed in which the lumina were filled with polymorphonuclear leucocytes (Fig. 2). This purulent cryptitis was usually not

associated with areas of ulceration and was frequently seen in zones in which the mucosa was intact and the inflammatory reaction in the surrounding tissue was not particularly marked. Occasionally, isolated abscesses were seen, containing in their centers necrotic remnants of a crypt. Frequently noted in the mucosa were scattered areas in which the normal architecture was completely destroyed and replaced by rather loose fibrous tissue infiltrated with chronic inflammatory cells.

Inflammatory polypoid hyperplasia was observed in 14 specimens (Fig. 3a and b). Malignant change was not seen.

The muscularis mucosae.—A consistent finding was that of disorganization and separation of the muscle bundles by edema and fibrosis. Frequently the muscle fibers over areas of varying lengths were completely destroyed and replaced by loose or dense fibrous tissue infiltrated with plasma cells and lymphocytes.

The submucosal lesion.—Inflammatory cellular infiltration was a prominent feature. Usually it was more or less diffuse, but occasionally it was focal and perivascular in location. The cells consisted mostly of plasma cells, lymphocytes, and epithelioid cells with varying admixtures of eosinophils and polymorphs. Subacute and acute inflammatory abscesses were observed infrequently. Edema, congestion of vessels, and dilatation of lymphatics were not prominent features.

Hyperplasia of the lymphoid tissue was observed in 15 of the 25 specimens. The lymph follicles were frequently large, and their germinal centers showed rather marked cellular activity.

It was in this stratum of the intestinal wall that the granulomatous aspects of the lesions were most apparent. Noncaseating giant cell systems were observed in 11 of the 25 specimens. These systems varied greatly in size and consisted of central accumulations of epithelioid cells surrounded by an admixture of lymphocytes, plasma cells, and epithelioid cells (Fig. 4). Giant cells were usually present, located most often in the center of the system but frequently at the periphery. They varied greatly in size and in number of contained nuclei. The nuclei were usually located around the periphery or at the poles, but it was not unusual to see them scattered throughout the cytoplasm. As a rule, there was no concentric lamination of the various cells making up the giant cell systems. No foreign bodies were seen in or adjacent to the giant cells.

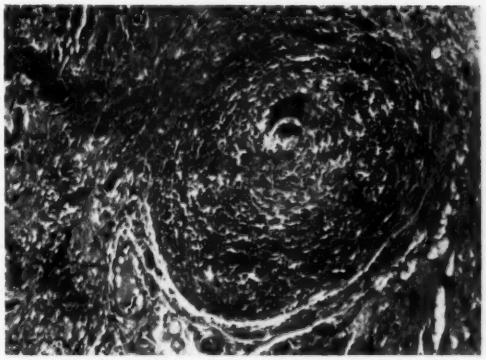


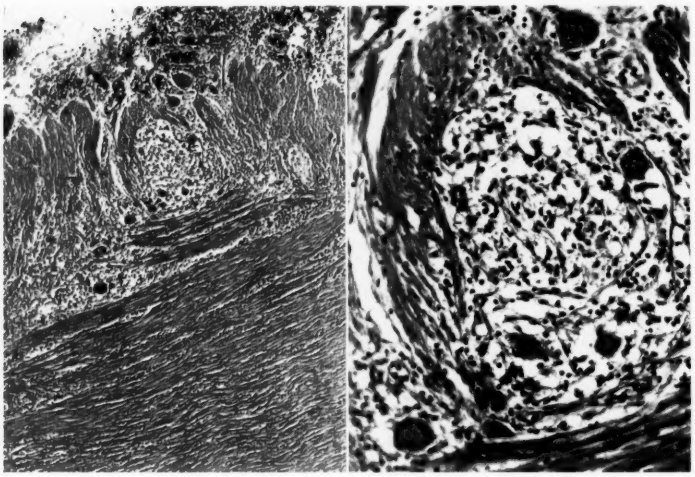
Fig. 4. Section through the wall of the colon showing a noncaseating giant cell system located in the submucosa. Note the extensive scarring of the muscularis propria. Hematoxylin and eosin, ×74.

There was definite thickening of the submucosa in 14 specimens. This was due to fibrosis and excessive deposition of fat. In scattered areas of small extent, however, the submucosa was nonexistent, the muscularis mucosae fusing directly with the muscularis propria.

The muscularis proprial lesion.—The most prominent finding in this stratum of the intestinal wall was diffuse and focal inflammatory cell infiltration. The cells consisted largely of plasma cells and eosinophils with varying numbers of epithelioid cells.

Well defined giant cell systems, located between the inner and outer muscular layers, were observed in 5 specimens, in 1 of which they were seen in the outer muscular layer as well (Fig. 5a and b). In 3 instances there was apparent destruction of the ganglion cells of the myenteric plexus by these systems. They were in all respects similar to those in the submucosa. Again, no foreign bodies were detected.

Active lymphoid follicles, located between the inner and outer muscular layers, were observed in 2 specimens. In 5 specimens the myenteric nerve plexuses appeared unusually prominent and numerous. Varying degrees of



a b

Fig. 5. a, Section through the wall of the colon showing noncaseating giant cell systems between the inner and outer muscle layers and in the outer muscle layer. Hematoxylin and eosin, ×37. b, Higher magnification of a, showing well defined giant cell systems in the muscle layer. Hematoxylin and eosin, ×148.

scarring of the muscularis propria (Fig. 4) were noted in 8 specimens, and in 1 there was extensive replacement of the muscle bundles by fat. Hypertrophy of muscle bundles was not seen.

The subserosal lesion.—Thickening of the subserosa by fibrous and adipose tissue was observed in 18 specimens. Diffuse and focal chronic inflammatory cell infiltration was prominent in 17 specimens. No consistent perivascular distribution of cells was noted. Accumulation of lymphocytes to form lymphoid follicles with active germinal centers was seen in 11 specimens. In 8 specimens giant cell systems similar to those described in other strata of the bowel wall were noted.

The lymph nodes.—Lymph nodes from the adjacent mesentery were found and examined in 20 of the 25 specimens. These consistently showed evidence of chronic inflammation as manifested by hyperplasia of the reticuloendothelial cells and sinus catarrh. Giant cell systems were seen in the lymph nodes from 4 specimens (Figs. 6 and 7); in 1 specimen the lymph nodes contained histiocytic tubercles without giant cells. In approximately one-third of the specimens the lymph nodes contained scattered small foci of hyalinized fibrous tissue, roughly spherical in shape. These may represent healed or fibrotic tubercles.

The healing process.—Evidence of healing was frequently found in close proximity to areas of active disease. Such evidence consisted of zones in the mucosa where there were few or no glands, merely fibrous tissue of varying degrees of maturity, showing varying degrees of chronic inflammatory cell infiltration, and covered by a single layer of mucous-secreting cells. Mitoses occasionally were visible in these epithelial cells. In other areas there was no fibrosis of the mucosa, but it contained very few glands and showed only slight increase in cellularity. Extensive scarring of the muscularis mucosae, submucosa, and muscularis propria constituted further evidence of healing.

Gross features of the ileal lesion. The length of ileum involved varied from the extremes of 4 to 25 centimeters with an average of 11.66 centimeters for the 7 specimens showing ileal extension. Thickening of the wall of the ileum was present in each specimen; there were no areas in the involved segment which were con-

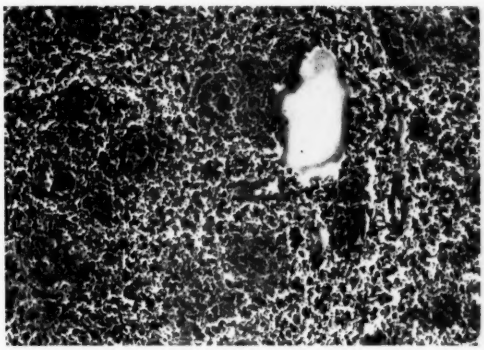


Fig. 6. Section from a mesenteric lymph node showing many tubercles with and without giant cells. Hematoxylin and eosin, ×74.

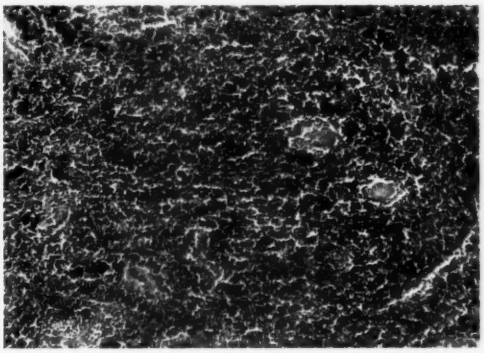


Fig. 7. Section taken from a mesenteric lymph node showing the presence of giant cells. Hematoxylin and eosin, ×74.

sidered as being of normal thickness. The thickness of the normal terminal ileum is from 3 to 4 millimeters. In 4 specimens the thickness of the wall of the involved ileum measured from 6 to 9 millimeters, in 2 specimens from 10 to 12 millimeters, and in 1 from 5 to 13 millimeters. The size of the lumen was considered normal in only 1 specimen; in the remaining 6, the lumen was considered markedly narrowed in 4 and moderately narrowed in 2. In all but 1, thickening of the wall took place at expense of the size of the lumen.

Ulceration of the mucous membrane was apparent grossly in 6 specimens. The ulcers varied in size from 3 to 10 millimeters, were linear and ovoid in configuration, shallow in depth, and exhibited very little undermining of the margins. In 3 specimens the ulceration was present over the entire circumference of the wall but was most marked along the mesenteric border. In the remaining 3 specimens the ulceration was present only along the line of mesenteric attachment. Between areas of ulceration the mucosa appeared hypertrophic and polypoid in 3 specimens, smooth and thin in 1, and normal in the remaining 2.

Transition from diseased to normal ileum was abrupt in 6 specimens, gradual in 1.

The lymph nodes from the mesentery of the terminal ileum were enlarged in 3 specimens, normal in the remaining 4.

Microscopic features of the ileal lesion. Ulceration of the mucous membrane was observed in all 7 specimens. In 5 of these the ulceration had not penetrated the muscularis mucosae; in 1 specimen ulceration had extended into the submucosa, and in 1 into the muscularis propria. The bases of the ulcers were covered by fibrin, necrotic material, and polymorphonuclear leucocytes. Adjacent to the bases of the ulcers were broad zones of acute and subacute inflammatory cells extending more deeply into the wall. Frequently, beneath these zones, were seen broad zones of dense fibrous tissue showing varying degrees of chronic inflammatory cell infiltration. Specific changes exhibited by the various layers of the ileal wall were as follows:

The mucous membrane proper.—The mucosal lesion was almost identical with that observed in the colon. Diffuse infiltration with plasma cells, histiocytes, eosinophils, and varying numbers of polymorphonuclear leucocytes was a prominent feature. Isolated areas of subacute and purulent cryptitis were observed, and in 1 specimen, subacute inflammatory abscesses. Occasional areas were seen in which the entire normal mucosal architecture was replaced by fibrous tissue infiltrated with chronic inflammatory cells.

Inflammatory polypoid hyperplasia was observed in 2 specimens.

The muscularis mucosae.—A consistent finding was disorganization and interruption of muscle bundles by fibrous tissue and, in scattered areas, complete replacement of muscle by fibrous tissue. Minimal infiltration with plasma cells and eosinophils was noted.

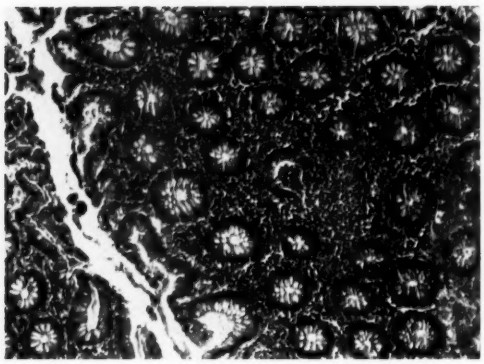


Fig. 8. Section through the wall of grossly normal ileum 3 centimeters proximal to the gross limit of the lesion. Note that one crypt is the site of acute purulent cryptitis and that immediately adjacent to it is a small abscess. Hematoxylin and eosin, ×74.

The submucosal lesion.—Inflammatory cell infiltration with plasma cells, lymphocytes, eosinophils, and small numbers of polymorphs was observed in each specimen. Such infiltration was usually diffuse but occasionally focal. In connection with the latter, no definite predilection for perivascular location was detected. Hyperplasia of the lymphoid tissue was seen in 5 specimens. Noncaseating giant cell systems, similar to those observed in the submucosa of the colon, were present in 2 specimens.

Thickening of the submucosa due to fibrosis and deposition of fat was noted in each specimen. Occasional areas were seen in which the muscularis mucosae fused directly with the muscularis propria, the submucosa having been completely destroyed.

The muscularis proprial lesion.—Small numbers of inflammatory cells, largely plasma cells and eosinophils and an occasional histiocyte, were seen between the muscle bundles in almost every specimen. Giant cell systems, located between the inner and outer muscular layers, were observed in 2 specimens. Accumulations of lymphocytes to form lymph follicles with active germinal centers were noted between the inner and outer muscular layers in 2 specimens. Undue prominence of the myenteric nerve plexuses was considered present in 1 specimen. No hypertrophy of muscle bundles was noted.

The subserosal lesion.—Thickening of the subserosa by fibrous and adipose tissue was observed in 6 specimens. Diffuse and focal chronic inflammatory cell infiltration was seen in all. Lymph follicles with active germinal centers were observed in 6 specimens. Giant cell systems were observed in 1 specimen.

The lymph nodes.—Lymph nodes from the adjacent mesentery were found in 6 of the 7 specimens. All showed chronic inflammation. Granulomas, with or without giant cells, were seen in the lymph nodes of 2 specimens.

The healing process.—Evidence of healing, similar to that already described in connection with the colonic lesion, was observed adjacent to and distant from areas of active disease.

Comparison of the lesions in the colon and ileum. Grossly and microscopically the lesions in the colon and ileum were very similar. The lesion in the colon, however, appeared more severe than that in the ileum. The ulcerative process was more widespread in the colon and the size of the individual ulcers tended to be larger. The presence of a purulent cryptitis and abscess formation in the wall was more often noted in the colon than in the ileum. In addition, the granulomatous character of the lesion appeared more pronounced in the colon.

Microscopic study of colon beyond the gross lesion. It was possible to obtain blocks of tissue from the wall of apparently normal colon at the 3 centimeter level distal to the gross confines of the lesion in 6 specimens, at both 3 and 6 centimeter levels distally in 7, and at 3 and 6 centimeter levels proximally in 2 specimens. Microscopic study of sections made from these blocks revealed no microscopic abnormality at the 3 and 6 centimeter levels proximal to the gross lesion nor at the 6 centimeter level distal to the gross lesion. Pathologic changes, however, were observed in 5 of the 13 specimens in which blocks were taken at the 3 centimeter level distal to the gross lesion. These changes were minimal and consisted of the following: (1) areas in the mucosa where the glands had been destroyed and replaced by connective tissue infiltrated with lymphocytes and plasma cells, (2) fibrous scarring of the submucosa, and (3) foci of lymphocytes and plasma cells in the muscularis propria.

Microscopic study of ileum beyond the gross lesion. Blocks were obtained from grossly normal ileum in 5 specimens in which the pathologic process ended in the cecum. In 2 specimens the length of the ileum permitted the taking of blocks at the 3 centimeter level only. In the remaining 3 it was possible to cut blocks at both 3 and 6 centimeter levels. Study of sections made from these blocks revealed no microscopic abnormalities at the 6 centimeter level. In 2 specimens, however, minimal pathologic changes were detected at the 3 centimeter level. These consisted of replacement of mucosal glands in scattered areas by connective tissue infiltrated with eosinophils, lymphocytes, and histiocytes, and underlying submucosal scarring.

In 5 specimens in which the ileum was grossly involved, blocks were obtained at the 3 centimeter level proximal to the gross limit of the lesion in 4, and at both 3 and 6 centimeter levels in 1 specimen. Microscopic abnormality was detected in only 1 specimen at the 3 centimeter level; this consisted of acute purulent cryptitis with abscess formation deep in the mucosa (Fig. 8).

SUMMARY

The gross and microscopic features of the lesion in regional (segmental) colitis, as observed in 25 resected specimens, are described. The predominant gross features are ulceration of the mucous membrane and thickening of the wall. Microscopically the lesion is nonspecific subacute and chronic granulomatous inflammatory process involving the entire thickness of wall. Our observations differ from those of Warren and Sommers, who stated that, in nonspecific ulcerative colitis as a whole, the inflammatory process is exudative and reparative, without any granulomatous tendencies. The lesion in the ileum is practically identical to that in the colon. Microscopically the lesion does not extend more than 6 centimeters beyond the gross limits of the lesion. Failure to excise widely enough beyond the gross limits of the lesion would not seem, then, to be a significant factor in recurrence.

Gross mesenteric lymphadenopathy is seen only occasionally and is never marked. Focal granulomas are present in the mesenteric lymph nodes, but the granulomatous nature of the lesion is not as uniformly apparent nor as marked as in the wall of the intestine.

It is suggested that the earliest pathologic lesion in the intestine may be a purulent cryptitis, followed subsequently by microscopic abscess formation and ulceration of the overlying mucosa.

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EXPERIMENTAL STUDY OF PULMONARY HISTOPATHOLOGY FOLLOWING POSITIVE AND NEGATIVE PRESSURE RESPIRATIONS

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THE development of Crafoord's spiropulsator in Sweden (1) and of the Mautz respirator in this country has been followed by increasing clinical use of automatic respirators. Recently, interest has been aroused regarding the possible beneficial effects of inserting a negative pressure phase in the respiratory cycle. Experimental studies by physiologists and clinicians interested in cardiopulmonary dynamics have established the beneficial effects of negative endotracheal pressure in relation to the return of blood to the heart. Brecher and Hubay and associates, using direct flow measurements in dogs, have described significant increases in venous return through the superior and inferior venae cavae with negative endotracheal pressure in the closed chest. Birnbaum and Thompson have shown that a blood column can be circulated in the absence of cardiac activity with a respirator employing intermittent positive and negative pressure respirations.

Because of the potential clinical application of negative endotracheal pressure in the fields of surgery and anesthesia, reports are appearing in the literature concerning the pulmonary changes occurring during intermittent positive and negative pressure respirations. The chief opponent to the use of negative pressures in automatic respirators has been Henderson who believes that in thoracotomies moderate intermittent positive pressure is the optimum method of pulmonary ventilation, "but negative pressure is certainly contraindicated." Using intermittent positive and negative pressures of 31 centimeters of water over a period of 22 to 90 minutes in 3 dogs, Henderson observed "a subsequent progressive fall of arterial pressure and death within a few hours thereafter." In previous experiments using more extreme positive and negative respirations he found that natural breathing failed to return and the animals died in anoxia. However, he also reports the use of lower pressures (15 cm. water) in similar experiments without serious harm to the animals. Schwerma and Ivy, in a review of the literature, were unable to find evidence indicating that the lung is damaged by alternating positive and negative pressure of +14 and −9 millimeters of mercury. This was verified in similar experiments of their own. Coryllos, Birnbaum and Thompson, and Steinberg have employed automatic positive and negative pressure respirators without significant pulmonary changes. Handford used intermittent positive and negative pressure respirations of +13 and −9 millimeters of mercury in restoring dogs from asphyxia produced by curare poisoning and found no evidence of lung damage after periods averaging 45 minutes. The present study was undertaken because there continues to be some question as to the nature of the histologic changes occurring in lungs subjected to intermittent positive and negative pressure respirations, and because it appeared necessary to determine the effects in the open chest as well as in the closed.

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PROCEDURE

Forty-four healthy adult mongrel dogs weighing 12 to 22 kilograms were anesthetized with intravenous nembutal by using 30 milligrams per kilogram of body weight. None of the animals received premedication. Each animal was placed on his back and intubated with a No. 40 F. endotracheal tube with a Magill cuff inflated sufficiently to prevent escape of air around the tube. While breathing

spontaneously a midline incision over the trachea was made with a cautery knife and the left common carotid artery isolated and ligated distally. A large brass cannula filled with heparinized saline was then passed down the artery into the aorta, and connected to a Statham pressure transducer. In some animals a cannula was passed via the right jugular vein into the superior vena cava and connected to a Statham low pressure transducer. The endotracheal tube was then connected to an experimental respirator which is similar to the one described by Mautz except for a hand switch incorporating a Venturi device to effect negative pressure. The hand switch allowed any desired cycle of positive, negative, or atmospheric pressure to be applied to a standard 5 liter bag incorporated in a plastic enclosure. Pressures were varied and controlled by water manometers in an early model, and by needle valves and weighted "pop off" valves in a later modification of the respirator. Endotracheal pressures were obtained by a Statham strain gauge attached to a side arm adapter at the proximal end of the intratracheal tube. The ventilating agent in all experiments was oxygen, delivered by a Heidebrink gas machine. In the open chest series, the thorax was opened through the left fifth interspace using the electrosurgical knife. Controlled respirations were begun when the pleura was opened. In those animals offering resistance to, or breathing against the respirator during the experiment, anesthesia was deepened, or they were given curare intravenously, in order to gain full control of the respiratory cycle. The period of artificial respiration during the first 9 experiments was 4 hours. Because damage after a 4 hour period was no greater than after 2, the remaining 31 animals were respirated for 2 hour periods.

Arterial blood pressure, central venous pressure, and endotracheal pressures were recorded simultaneously on a Sanborn direct writing 4 channel oscillograph. Arterial blood samples were drawn at hourly intervals for determination of carbon dioxide by the Van Slyke technique. The experimental studies were classified under the major categories of closed chest and open chest, and further subdivided into the following groups:

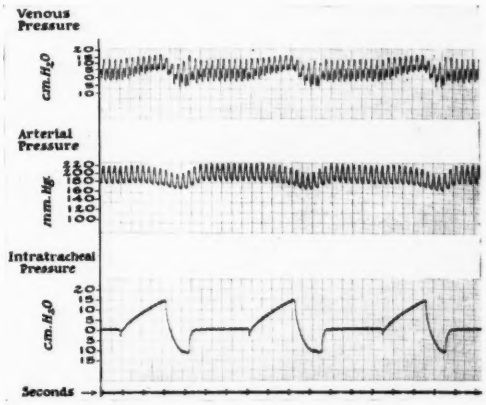

Fig. 1. Typical record showing simultaneous endotracheal pressure, arterial pressure, and central venous pressure in an animal subjected to intermittent positive and negative pressure respirations of +15, −10 centimeters of water in the closed chest.

Closed chest—(1) 2 control animals which were anesthetized, intubated, and allowed to breathe spontaneously over a period of 2 hours; (2) 5 animals subjected to intermittent positive pressure respirations; (3) 11 animals subjected to intermittent positive and negative pressure respirations; (4) 4 animals subjected to intermittent positive and negative pressure respirations were allowed to recover. Roentgenograms of their chests were made prior to and 24 and 48 hours following the period of study.

Open chest—(1) 3 animals subjected to intermittent positive pressure respirations; (2)

TABLE I.—SUMMARY OF PATHOLOGIC CHANGES OCCURRING IN LUNGS SUBJECTED TO POSITIVE PRESSURE ONLY WITH CHEST CLOSED

No.	Pressure (cm. H_2O)	Degree	Evaluation
1	+10; A	+	No serious pathologic changes
2	+10; A	+	No serious pathologic changes
22	+15; A	+++	Focal hemorrhage
39	+40; A	+	Bronchopneumonia, emphysema
41	+40; A	+	Pneumonitis, emphysema
42	Control	++	Focal hemorrhage
43	Control	+	No serious pathologic changes

Two control animals, intubated only and allowed to breathe spontaneously, are included.

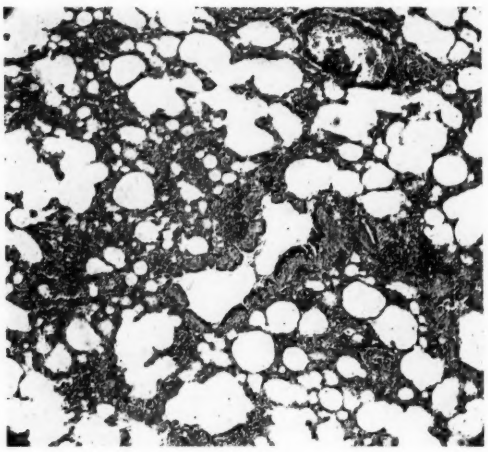

Fig. 2. Lung of control animal not subjected to artificial respirations showing emphysema and intra-alveolar hemorrhage.

19 animals subjected to intermittent positive and negative pressure respirations.

In both the closed chest group and the open chest group, the maximum endotracheal pressure range was from +40 to −40 centimeters of water.

The method of sacrifice has been shown to be important. In this series, at the termination of each experiment the animals were given a rapid intravenous injection of 10 to 15 cubic centimeters of nembutal, which usually resulted in cessation of functional cardiac activity in 1 to 2 minutes. The entire anterior chest plate was then removed by dividing the ribs at the costochondral junction. The lungs were inflated to a position of mid-expansion and the trachea below the Magill tube occluded with a clamp. The hilus of each lung was then ligated with umbilical tape and the heart and lungs removed together. After removal from the heart, the lungs were weighed, sectioned for gross examination, and fixed in formalin. Following adequate fixation, 24 hour paraffin sections were made of each lobe, hilar regions, and any area of suggestive hemorrhage or other pathologic change.

TABLE II.—SUMMARY OF PATHOLOGIC CHANGES OCCURRING IN LUNGS SUBJECTED TO POSITIVE AND NEGATIVE PRESSURE IN CLOSED CHEST

No.	Pressure (cm. H_2O)	Degree	Evaluation
3	+10; −5; A	+	Slight focal hemorrhage
18	+10; −5	+	Slight focal hemorrhage
4	+10; −10	+	No serious pathologic changes
15	+10; −10	+	No serious pathologic changes
23	+10; −15	+++	Focal intra-alveolar and periarterial hemorrhage
24	+10; −15	++	Focal intra-alveolar hemorrhage
25	+10; −15	+	Focal bronchopneumonia
26	+10; −20	+	No serious pathologic changes
37	+10; −34	+++	Interstitial, intrabronchial, and peribronchial hemorrhage
38	+10; −40	++	Interstitial hemorrhage
44	+15; −40	++++	Edema and marked hemorrhage

RESULTS

The respirator used in this study delivered accurate pressures during both the positive and the negative phases throughout the 2 hour cycle. It was not necessary to shift to another machine or "bag squeeze" in order to maintain accurate or adequate pressures in any of the experiments. Occasionally pressure would build up in the closed system so that the endotracheal pressure would not return to the atmospheric level, but this could quickly be remedied by disconnecting the tubing on the inspiratory side of the gas machine. Figure 1 is a typical record showing the endotracheal pressure contour tracing delivered by the experimental respirator. The central venous and aortic pressures during the period of study remained relatively normal, showing only the expected pressure variations known to occur with respiration. Although aortic and central venous pressures were obtained in many animals, it is not the purpose of this study to evaluate the circulatory changes during controlled respiration. A résumé of the pulmonary changes in both open and closed chest groups during various endotracheal pressures is presented in Tables I through IV.

The results of the present study substantiate the work of Orth in that microscopic changes were observed in all sections of lungs examined, including control animals not subjected to artificial respiration. The minimal changes appearing in many of the sections ex-

amined may be due to trauma at the time of removal of the lungs, delay in formalin fixation, and changes during death of the animal. These changes, which are listed in the tables as 1 plus and 2 plus are not considered to be the effects of positive or negative pressure. All gross hemorrhages and those microscopic hemorrhages, which were large or appeared in more than one section, were classed as severe and listed as 4 plus. Sections showing only small focal areas of alveolar hemorrhage with other changes such as pulmonary edema and emphysema were listed as 3 plus. All 3 plus and 4 plus changes were considered to be due to the effects of controlled respirations.

In Table I are the results of the closed chest group undergoing intermittent positive pressure respirations. None of the sections examined microscopically in this group revealed serious pathologic changes, although slight focal, intra-alveolar or peribronchial hemorrhages were noted in a few. Atelectasis and hyperemia are not considered important findings because in many instances some collapse of the lungs was inevitable following removal from the chest, and the lungs were not fixed by injection of formalin into the bronchi. It was observed that 2 animals of this group (Nos. 39 and 41) showing minimal pulmonary changes were those in which the highest pressures (+40 cm. water) were used. The lungs of the 2 control animals which had been anesthetized and allowed to breathe spontaneously for 2 hours were found to have slight changes consisting of focal hemorrhage and emphysema (Figs. 2 and 3).

In Table II are listed the pulmonary changes in the second group. The pathologic changes were slight and were otherwise similar to those found in group 1, with the exception of 3 animals which were among those subjected to greater negative pressures. It should be noted, however, that the pulmonary changes in animal 38 subjected to +10, −40 centimeters of water pressure were classified as slight (Figs. 4 and 5).

In Table III may be seen the results in 3 animals subjected to thoracotomy and intermittent positive pressure respirations. Two of these were respirated with 10 centimeters of water positive pressure, and the changes

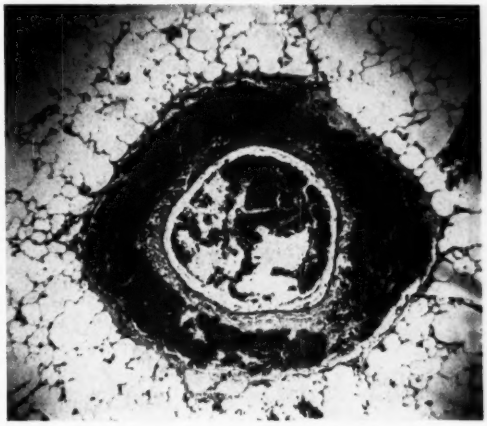

Fig. 3. Lung of control animal not subjected to artificial respirations showing perivenous hemorrhage.

classified as slight. The third, however, was subjected to a pressure of +40 centimeters of water, and the lungs of this animal revealed severe changes with gross hemorrhages, measuring 1 to 2 centimeters in diameter, and, microscopically, massive intra-alveolar hemorrhages, pulmonary edema, and emphysema. From the standpoint of microscopic pulmonary changes the difference between the application of high positive pressure in the open chest and the use of the same pressure in the closed chest is striking.

In Table IV is a series of 19 dogs subjected to thoracotomy and intermittent positive and negative pressure respirations. The pathologic changes are similar to those previously described but are quite inconsistent from pressure to pressure. The lungs of several animals subjected to the minimum negative pressure (−5 cm. of water) and 1 with the maximum negative pressure (−40 cm. of water) revealed only slight or moderate changes (Fig. 6) while

TABLE III.—SUMMARY OF PATHOLOGIC CHANGES OCCURRING IN LUNGS SUBJECTED TO POSITIVE PRESSURE ONLY IN OPEN CHEST

No.	Pressure	Degree	Evaluation
5	+10; A	++	Focal hemorrhage
6	+10; A	+	Slight focal hemorrhage
40	+40; A	++++	Marked intra-alveolar hemorrhage and edema

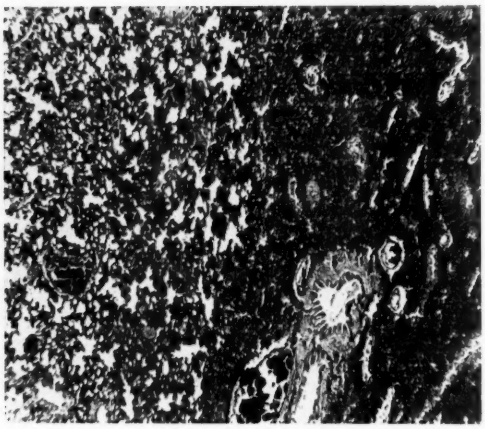

Fig. 4. Lung of animal 44 subjected to intermittent positive and negative pressure respirations of +10, −40 centimeters of water in the closed chest. This view shows the transition from lung containing numerous air-containing alveoli to an area of massive hemorrhage in which the alveoli are completely filled with blood.

those respirated at intermediate pressures had changes varying from minimal to severe. Again, there appears to be a difference in the degree of pulmonary changes using high negative pressures in the open chest as compared to the closed chest. In several animals of this group part of the pathologic picture may be attributed to technical difficulties. There seems to be no definite correlation between the rising negative intratracheal pressure and the increasing pulmonary damage in this group.

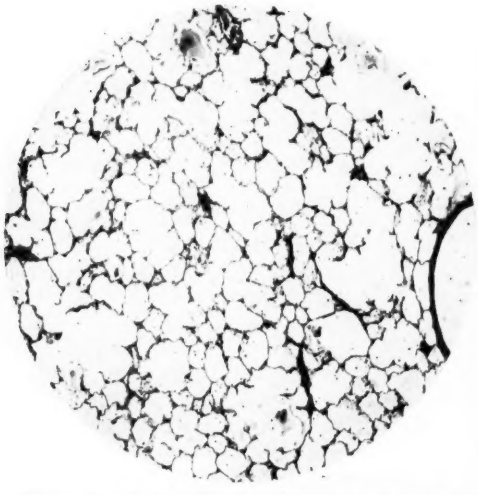

Fig. 5. Lung of animal 38 subjected to intermittent positive and negative pressure respirations of +15, −40 centimeters of water in the closed chest. The findings consist only of slight emphysema and edema. Other sections show slight focal hemorrhages. (Compare with Fig. 4.)

The study includes a series of 4 animals which were not sacrificed at the termination of the experiments, but had roentgenograms of the chest before and after a period of intermittent positive-negative atmospheric respirations under anesthesia. All 4 animals were respirated with 10 centimeters of water positive pressure, and a terminal rest phase at atmospheric pressure. The negative pressures used were −5 centimeters of water in 1, and −10 centimeters of water in the remaining 3 animals. There were no radiographic changes in any of these animals following the period of study. Following return of the animals to their cages all recovered completely without evidence of pulmonary damage.

DISCUSSION

Experimental studies concerning the effects of various pressures in the tracheobronchial system on pulmonary tissue have been confined in the past to closed chest animals. The relative safety of intermittent positive and negative pressure respirations has been reported briefly by a number of investigators. However, there are but a few carefully controlled experimental studies, the primary objective of which has been to correlate lung damage with various pressures in the airway. Schwerma and Ivy found minor pathologic lung changes in 6 animals (bronchopneumonia being present in 2) in a group of 20 dogs aspirated over a period of time ranging from 1 to 3 hours, and sacrificed after 3 days. Orth described pathologic changes in the lungs of dogs which were similar in both the control group and in the animals subjected to maximum positive (+76 mm. of mercury) and negative (−35 mm. mercury) pressure. In all groups regardless of method, the microscopic changes consisted of areas of atelectasis, congestion, bronchial and alveolar hemorrhage, and bronchial spasm. He concludes: "Probably the most outstanding feature of this study was the

TABLE IV.—SUMMARY OF PATHOLOGIC CHANGES OCCURRING IN LUNGS SUBJECTED TO POSITIVE AND NEGATIVE PRESSURES IN OPEN CHEST

No.	Pressure	Degree	Evaluation
9	+10; −5; A	+	Bronchopneumonia
14	+10; −5	+	Slight focal hemorrhage
19	+10; −5	+	Slight focal hemorrhage
20	+10; −5	+	Slight focal hemorrhage
21	+10; −5	++	Focal hemorrhage
30	+15; −5	++	Focal hemorrhage
7	+10; −10; A	++++	Intra-alveolar and intra-bronchial hemorrhage
8	+10; −10; A	++++	Intra-alveolar and intra-bronchial hemorrhage
16	+10; −10	+	No serious pathologic changes
31	+15; −10	++	Focal hemorrhage
32	+15; −10	++	Intrabronchial and intra-alveolar hemorrhage
36	+20; −10	++	Bronchopneumonia; focal hemorrhage
27	+10; −15	+++	Intrabronchial and intra-alveolar hemorrhage; edema
28	+10; −15	++	Focal hemorrhage
29	+10; −15	++	Intra-alveolar and intra-bronchial hemorrhage
33	+15; −15	+	Slight focal hemorrhage
34	+15; −15	++++	Marked hemorrhage
35	+15; −20	++	Intra-alveolar and intra-bronchial hemorrhage
45	+15; −40	++	Edema, emphysema

fact that there was evidence of abnormality in every section of lung examined."

The most significant feature of the present study is the difference in the effect of high positive and negative endotracheal pressure in the closed chest compared to the open chest. High positive pressure (40 cm. of water) was apparently well tolerated in the closed chest, the changes being no more severe than in the control animals, whereas in the open chest pressure of the same magnitude caused severe hemorrhage. The most apparent causative factors in producing such changes in the open chest are intermittent overdistention, exposure of the lungs over a prolonged period, and trauma at the site of thoracotomy. On the other hand the higher negative pressures were poorly tolerated in the closed chest. In the open chest the degree of pulmonary damage did not correspondingly increase with negative

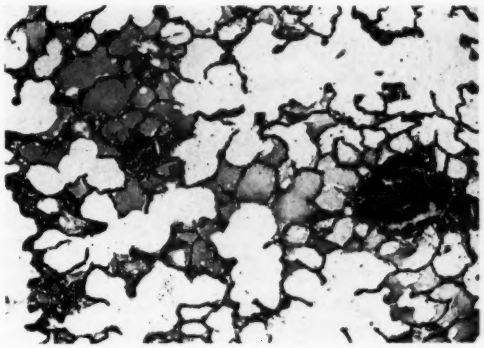

Fig. 6. Lung of animal 45 subjected to intermittent positive and negative pressures of +15 and −40 centimeters of water with the chest open. This section shows emphysema which was common in all animals regardless of the pressures employed (compare with Fig. 2) and focal pulmonary edema which was more frequently encountered following the use of high negative pressure.

endotracheal pressures more forceful than 10 centimeters of water. The significant changes which occurred were in the intermediate pressure range (−10 to 15 cm. of water) with minimal changes in the 2 animals subjected to the greatest negative pressure (Table IV).

In the open chest with complete collapse of the lung, it is possible that the application of 10 to 15 centimeters of water negative pressure to the airway causes collapse of the bronchioles, thereby preventing effective transmission of higher pressures to the periphery. In the closed chest the lung is maintained in a partially expanded position by the physiologic negative intrathoracic pressure. This may allow more effective transmission of the higher negative pressures to the pulmonary tissue resulting in more serious changes. Observation of the lungs subjected to negative pressures revealed a definite rebound of lung tissue immediately following the negative pressure phase. The maximum recoil occurred with −5 to −10 centimeters of water. Negative pressure greater than this caused no further collapse of pulmonary parenchyma, and no increase in the elastic recoil of the lungs.

The results of this study using an experimental respirator show no evidence of significant pulmonary changes using negative pressure of −5 centimeters of water. Negative pressures greater than −10 centimeters of

water may be attended by more serious damage, particularly in the closed chest.

SUMMARY

1. An experimental respirator employing various intermittent positive and negative pressures was used in 44 healthy adult mongrel dogs over a 2 to 4 hour period, in both the open and closed chest, to determine the occurrence of pathologic pulmonary changes.

2. Pulmonary changes were observed in all sections of lungs examined including control animals not subjected to artificial respiration. The minimal changes observed in most sections are attributed to trauma during removal of the lungs, delay in formalin fixation, and changes during death of the animal.

3. Intermittent positive pressures up to 40 centimeters of water were well tolerated in the closed chest. In the open chest, intermittent positive pressure of 40 centimeters of water caused severe damage owing to repeated overdistention, trauma at the thoracotomy opening, and exposure.

4. High negative endotracheal pressures in the closed chest caused more severe damage than in the open chest presumably owing to the direct transmission of this pressure to the lung parenchyma. It is thought that in the open chest, effective high negative endotracheal pressures cannot reach the lung parenchyma owing to the complete collapse of the bronchioles at lower pressures.

5. No significant changes were observed by using negative pressures of −5 centimeters of water.

6. The most favorable endotracheal pressures allowing effective pulmonary ventilation with minimal lung damage of 15 to 20 centimeters of water positive pressure and 5 centimeters of water negative pressure.

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VALVULOTOMY FOR THE SURGICAL RELIEF OF AORTIC STENOSIS

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THE first attempt to relieve aortic valvular stenosis was by Tuffier in 1913. However, little work in developing methods for treating this deformity evolved until the experimental and clinical investigations of Smithy and co-workers (7, 8). The work of Bailey, Glover, O'Neill, and Redondo Ramirez (1) and other associates (3, 6) further elucidated some of the problems associated with the surgical treatment of this disease. Brock and Daniel and Scott also reported their experiences with procedures to open the stenotic valve. Bailey and his associates (1) demonstrated that the valve should be dilated rather than cut, and allowed to tear, preferably along the fused commissures. In this report, problems encountered and surgical considerations in relieving aortic stenosis in a group of patients are presented.

SELECTION OF CANDIDATES FOR AORTIC VALVULOTOMY

In selecting patients to undergo aortic valvulotomy, only those with a relatively pure aortic stenosis should be considered for operation by present techniques. Many of these patients have a diastolic murmur representing some degree of insufficiency. However, if significant insufficiency is present, valvulotomy should not be performed. The diastolic pressure should be normal or only slightly diminished, and there should not be excessive left ventricular enlargement, which characteristically accompanies aortic insufficiency. As in mitral stenosis, age is not necessarily a determining factor in the selection of patients for operation, but those older than 50 or 55 years should be considered cautiously. Those who have congenital aortic or subaortic stenosis should be operated upon when the diagnosis is made, if it can be determined by electrocardiographic tracings and fluoroscopic examination of the left ventricle that strain and enlargement of this cardiac chamber exist. Calcification of the valve does not contraindicate operation. On the contrary, the majority of suitable candidates for aortic valvulotomy have calcified aortic valves.

A classification of patients with aortic stenosis according to the severity of symptoms follows:

Group I—those patients with a murmur characteristic of aortic stenosis only.

Group II—those with a murmur, palpitation, easy fatigability, and mild dyspnea.

Group III—those with the more advanced symptoms of dizziness, angina, and syncope.

Group IV—those with any of the above symptoms associated with an additional defect, such as mitral stenosis.

Group V—those with advanced disease who have congestive failure and peripheral edema in addition to the symptoms in the other groups.

At present we believe that groups II, III, IV, and V should be considered as candidates for aortic valvulotomy. Those in groups III, IV, and V, particularly, should be given digitalis and mercurial diuretics along with a regimen of bed rest prior to operation to achieve the best possible condition.

It is likely that young patients who have an intense murmur only, are otherwise asymptomatic, and have a narrow pulse pressure and low systolic blood pressure might be considered as candidates for operation in the future when the operative procedure has been proved satisfactory. It is in this type of patient, who

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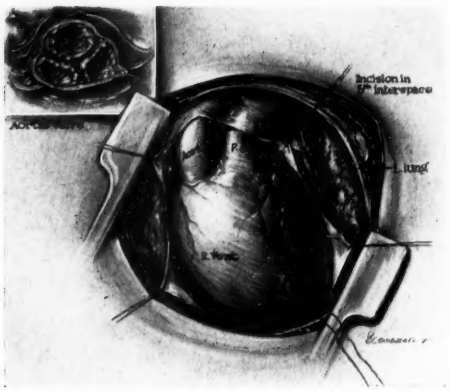

Fig. 1. Operative exposure through an anterolateral incision in the fifth left intercostal space. The pericardium has been opened and a purse-string suture placed in the myocardium of the left ventricle.

does not have calcification of the valve and whose valve is more likely to split along the fused commissure resulting in a competent valve, and whose left ventricular reserve has not been depleted, that a good result can be expected.

Contraindications to operation include: (1) marked aortic insufficiency, (2) evidence of poor myocardial reserve, (3) complete heart block, (4) subacute bacterial endocarditis, (5) acute rheumatic fever. Age is not a contraindication per se but depends upon the degree of cardiac enlargement, the duration of symptoms, and other factors.

SURGICAL TECHNIQUE

The patient is placed supine on the operating table and induced with sodium pentothal or cyclopropane. Endotracheal anesthesia as required is used throughout the operation. Curare-like drugs may be necessary to control movement of the mediastinum. The left side of the chest is elevated about 20 degrees and prepared aseptically. The incision is made over the fifth intercostal space, extending from the left border of the sternum to the posterior axillary line. The fifth costal cartilage is divided adjacent to the sternum. By spreading the ribs widely the entire ventricular portion of the heart is exposed and one has no difficulty in palpating the region of the aortic valve ring (Fig. 1). The pericardium is incised from a point just above the apex to its reflection on the aorta. A purse-string suture of No. 2 braided silk is placed in an avascular portion of the left ventricle, approximately 3 centimeters from the apex, which has been infiltrated with 1 per cent novocain. Pressure measurements are then made in the left ventricle and aorta by means of a needle connected to a catheter and a strain gauge manometer. A short transverse stab wound is made in the ventricle within the purse string and the valvulotome is inserted through the stab wound and passed along the septum into the stenotic valve (Fig. 2). By placing a hand on the aorta just above the valve ring one can feel the end of the dilator pass into the aorta through the valve. The instrument is then expanded, thus opening the stenosed valve, at which time there is usually a sensation of sudden yielding (Fig. 3). Often the heart will become much slower for a short period, but occasionally the rate has become more rapid. The dilator is withdrawn and the purse-string suture is tightened sufficiently to control bleeding. The incision in the ventricle is sutured with several interrupted silk sutures of No. 00 silk, since finer silk tends to cut through the soft myocardium. While the dilator is within the heart it is important that the assistant controlling the purse-string suture by means of a Rumel tourniquet does not tighten it excessively. Pressures are again measured in the left ventricle and the aorta (Fig. 4). The pericardium is closed loosely with interrupted sutures, and a small window of pericardium is excised in the most dependent portion posteriorly to allow adequate drainage. A Foley bag catheter is placed in the midaxillary line, 2 intercostal spaces below the incision. Five hundred thousand units of penicillin are placed in the chest cavity. The wound is closed in layers with interrupted silk sutures.

In the presence of an additional lesion such as mitral stenosis, until recently the chest has been entered through a posterolateral thoracotomy incision in the fifth intercostal space. However, poor risk patients with combined stenotic lesions do not tolerate the lateral position as well as the supine position, and more recently these patients have been ex-

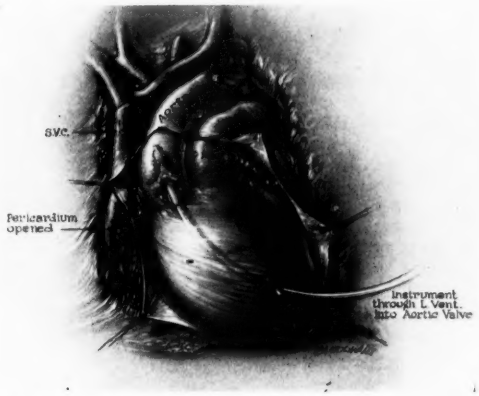

Fig. 2. The valvulotome has been inserted into the valve through a stab wound in the left ventricle.

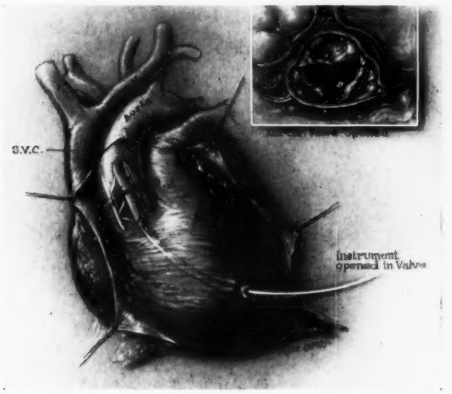

Fig. 3. The valvulotome is expanded and the stenosed aortic valve is dilated.

plored through anterolateral incisions in the fourth intercostal space. The fourth and fifth costal cartilages have been divided adjacent to the sternum, and the incision has been extended further posteriorly. Adequate exposure of the left auricle and the apical region can be obtained through such an incision. Aortic valvulotomy, as described previously, and the standard mitral commissurotomy have been performed.

CASE REPORTS

CASE 1. T.S.M., 31 year old male admitted to the Wadsworth Veterans Administration Hospital, was known to have a cardiac murmur since early childhood but no specific history of rheumatic fever. He had an episode of subacute bacterial endocarditis with embolization to the left eye 2½ years previously. In December 1951, he had an episode of syncope, and in the summer of 1952 a daily fever for 1 month. He had left anterior chest pain on exertion and moderate exertional dyspnea for several months.

Physical examination. Blood pressure was 100/80. The heart was not enlarged to percussion and auscultation. There were a systolic thrill and murmur over the aortic area. A systolic murmur was heard along the left sternal border. Fluoroscopy showed left ventricular enlargement.

On November 14, 1952, a transventricular aortic valvulotomy was performed. Since his discharge 32 days after operation he has had 3 episodes of unexplained fever, 1 of which was associated with a left pleural effusion. At the last follow-up, 15 months after discharge, he felt well, worked regularly, and required no medication.

CASE 2. D.H., 47 year old white male admitted to the Wadsworth Veterans Administration Hospital, had a 4 year history of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and exertional angina. In 1951 he was treated for a myocardial infarction.

Physical examination. Blood pressure was 130/100. There was a palpable systolic thrill over the aortic area, and a grade III harsh, systolic murmur, maximal in the left second interspace adjacent to the sternum, radiated over the entire precordium and into the neck. There was a grade I soft diastolic murmur at the apex. Roentgenograms showed left ventricular enlargement and a calcified aortic valve. Electrocardiograms showed a left ventricular enlargement with a strain pattern.

On March 30, 1953, transventricular aortic valvulotomy was performed. Considerable blood was lost but was quickly replaced. The procedure was well tolerated. Auricular fibrillation developed on the second postoperative day and was converted to a normal sinus rhythm with quinidine. The patient was discharged on the twenty-fourth postoperative day and was asymptomatic. He returned to his work but was killed in a barroom brawl 9 months after operation.

CASE 3. L.L., 41 year old female, was admitted to Saint John's Hospital with a diagnosis of aortic stenosis and coarctation of the aorta. The evidence of rheumatic fever in childhood was equivocal. The first symptoms occurred 1 year prior to admission and consisted of a feeling of constriction in her chest on exercise. Four weeks prior to admission she developed dyspnea on exertion, orthopnea, hemoptysis, and pulmonary congestion. She was digitalized 1 week prior to admission.

Physical examination. Blood pressure in the left arm was 118/70. In the left leg it was unobtainable. A systolic thrill was palpable over the aortic area and a loud, blowing, systolic murmur was heard in this region, which was transmitted to the left sternal border and into the carotid arteries. A femoral pulse

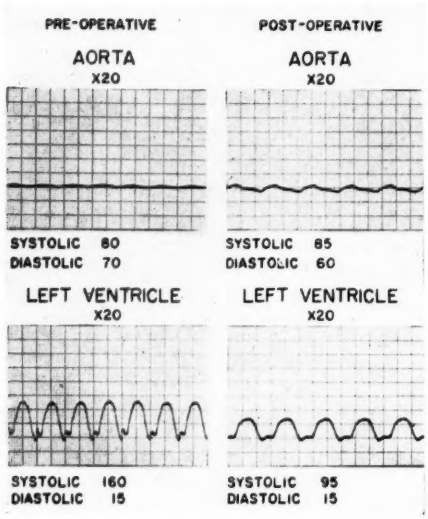

Fig. 4. Pressure tracing from left ventricle and aorta before and after valvulotomy. The pressure in the left ventricle equals that in the aorta after the valve is opened.

was felt in the right inguinal area, but was questionable on the left.

On April 29, 1953, a transventricular aortic valvulotomy was performed and the coarctation of the aorta was excised. The procedures were well tolerated and the patient was discharged on the twelfth postoperative day. She is asymptomatic and has returned to her work as an apartment house manager.

CASE 4. R.E., 41 year old male admitted to the Wadsworth Veterans Administration Hospital on April 14, 1951, had had 2 previous admissions for evaluation and treatment of acquired aortic stenosis. Symptoms were progressive fatigue and angina for 4 months' duration. A diagnosis of a small anterior myocardial infarction was made and after 8 weeks of medical treatment aortic valvulotomy was recommended.

Physical examination. The heart was moderately enlarged to the left. A rough, blowing, systolic murmur was heard over the aortic area, and in the neck.

On June 20, 1953, a transventricular aortic valvulotomy was performed. When the valvulotome was withdrawn, the purse-string suture tore out and severe hemorrhage resulted. Control of the ventricular wound was achieved with difficulty. Cardiac arrest ensued and was successfully treated with massage. For the first 24 hours postoperatively he had moderate hypotension and on the second postoperative day was digitalized for incipient failure. His blood pressure rose after digitalization and the remainder of his convalescence was uneventful. By the time of his discharge, he was taking long walks without angina. Recently he has had mild dyspnea on exertion.

CASE 5. W. P., 37 year old male admitted to Saint John's Hospital on May 28, 1953, had rheumatic fever at the age of 9. Dyspnea began 5 years ago, and 3 years ago he developed progressive angina. More recently he had moderately severe orthopnea. Ankle edema was noted for 1 week prior to admission.

Physical examination. The heart was moderately enlarged to the left. A systolic thrill was felt in the second right interspace immediately adjacent to the sternum. A rough, harsh, systolic murmur could be heard, maximal in this area, which radiated into the neck. On May 29, 1953, a transventricular aortic valvulotomy was performed. He was discharged on the tenth postoperative day and is working and asymptomatic at present.

CASE 6. W.H.B., 49 year old male admitted to Saint John's Hospital, had rheumatic fever at the age of 9. Four years ago he noted the onset of orthopnea and dyspnea and had 2 episodes of hemoptysis during the past year.

Physical examination. The heart was enlarged inferiorly and to the left. A loud, harsh, systolic murmur could be heard over the aortic area transmitted to the left basilar area and into the neck, and a blowing, systolic murmur was present along the left sternal border, at the apex, and transmitted to the axilla. A diastolic murmur was also present along the left sternal border. Occasional bigeminal rhythm and runs of ventricular extrasystoles were noted. A diagnosis of mitral and aortic stenosis was made.

On September 18, 1953, a transventricular aortic valvulotomy was performed, and because the left auricular appendage was extremely small the mitral valve was opened retrogradely with the valvulotome. It was not possible to tell how widely the mitral valve was opened. Postoperatively the patient progressed well. He was discharged on the tenth postoperative day, but died following a pulmonary embolus and congestive heart failure 3 months later.

CASE 7. E.G.G., 32 year old male admitted to the Wadsworth Veterans Administration Hospital, had no history of rheumatic fever but rheumatic heart disease was discovered in 1941. Since then he had marked fatigue, progressive dyspnea, and paroxysmal nocturnal dyspnea.

Physical examination. Blood pressure was 120/70. Point of maximal impulse was in the sixth intercostal space in the anterior axillary line. A diastolic thrill was present in the apical area and a systolic thrill in the aortic area. There was a loud, rough, diastolic rumble and a high pitched systolic blowing murmur at the apex transmitted to the axilla. There was a low pitched systolic murmur and a diastolic murmur over the aortic area and in the third left interspace. Roentgenograms showed cardiomegaly with left auricular and pulmonary artery segment enlargement. Electrocardiograms showed auricular fibrillation and digitalis effect.

A diagnosis of aortic and mitral valvular stenosis was made, and on September 18, 1953, aortic and mitral valvulotomies were performed. The left auricular appendage was filled with a large thrombus,

However, this was removed and no embolus occurred. The postoperative course was complicated by transient jaundice, which was thought to be caused by an incompatible transfusion. He was discharged on the nineteenth postoperative day.

CASE 8. M.D., 43 year old woman admitted to Los Angeles County Harbor General Hospital, had no history of rheumatic fever but symptoms of exertional dyspnea, which existed for 3 years prior to admission. Congestive failure, dyspnea, and orthopnea were present for the past year.

Physical examination. Blood pressure was 115/74. The heart was moderately enlarged to the left. A systolic thrill was palpable in the aortic area and a systolic murmur, which was transmitted to the neck, was also present. A diastolic murmur was present to the left of the sternum, transmitted to the apex. A long, blowing, presystolic murmur could be heard at the apex, and a soft systolic murmur was present in this area, transmitted to the axilla.

A diagnosis of aortic and mitral stenosis was made, and on September 22, 1953, a combined mitral and aortic valvulotomy was performed. Only minimal mitral insufficiency was present. Her postoperative course was uneventful and she has been without symptoms since operation.

CASE 9. A.V.O., 63 year old male admitted to the Wadsworth Veterans Administration Hospital, had had rheumatic fever since the age of 27. Dyspnea, paroxysmal nocturnal dyspnea, angina, orthopnea, several attacks of failure, and gradual weight gain began several months prior to admission.

Physical examination. Blood pressure was 150/98. Point of maximal impulse was in the sixth interspace 15 centimeters to the left of the midsternal line. There was a sinus rhythm. A palpable systolic thrill was present in the aortic area. There was a systolic murmur over the entire precordium, loudest at the aortic area. A whistling, diastolic murmur was present along the right sternal border. Roentgenograms showed cardiomegaly with left ventricular prominence. Electrocardiograms showed a first degree heart block and ventricular hypertrophy.

On September 25, 1953, an aortic valvulotomy was attempted through a sternum splitting incision. The valvulotome was introduced through the innominate artery and passed toward the aortic valve, at which point an irreversible cardiac arrest ensued.

CASE 10. H.E.S., 30 year old male admitted to the Wadsworth Veterans Administration Hospital, had a history of rheumatic fever in childhood and again 9 years prior to admission while in military service. Hemoptysis was first noted 8 years previously and repeated severe episodes ensued. He also complained of exertional dyspnea and paroxysmal nocturnal dyspnea.

Physical examination. Blood pressure was 110/74. The point of maximal impulse was in the sixth interspace in the anterior axillary line. At the apex a systolic thrill was palpable and diastolic and systolic murmurs were present. In the aortic area there was a systolic murmur transmitted to the neck. Electrocardiograms showed a first degree heart block and right ventricular hypertrophy. Roentgenograms showed left ventricular enlargement.

a b

Fig. 5. a, Photograph of aortic valvulotome in closed position. b, Dilating components in expanded position.

A diagnosis of mitral and aortic stenosis was made, and on November 13, 1953, first a mitral valvulotomy and then a transventricular aortic valvulotomy were performed. As the dilator was expanded in the aortic ring, the heart slowed immediately to a rate of 40 with apparently complete auricular and ventricular dissociation. About 6 hours after operation the rate gradually slowed until, when the rate reached the low 20's, the patient had convulsive seizures and lost consciousness. The electrodes of an artificial pacemaker were attached to the chest wall by Dr. J. Francis Dammann with the immediate production of an effective pulse of 60, and the patient regained consciousness. For the next 64 hours he was maintained on this pacemaker until, eventually, the action of his own pacemaker returned, first with an idioventricular rhythm and finally with a normal sinus rhythm. He was discharged 36 days following operation, considerably improved.

CASE 11. B.H., 14 year old male, was admitted to Saint John's Hospital without chest pain or dyspnea. A murmur was noted at birth. His activity was limited for the past 8 years. A diagnosis of congenital aortic or subaortic stenosis was made.

Physical examination. Blood pressure was 130/100. The heart was moderately enlarged to the left. There was a grade III rough, systolic murmur over the entire precordium with maximal intensity over the aortic area. Roentgenograms showed left ventricular enlargement.

On November 17, 1953, a transventricular aortic valvulotomy was performed. A harsh, systolic thrill, which was present in the aorta prior to the dilatation, was barely perceptible afterward. His postoperative course was uneventful except for a transiently elevated pulse rate and he was discharged on the tenth postoperative day.

CASE 12. J.S.I., 36 year old male, was admitted to Wadsworth Veterans Administration Hospital. He had had rheumatic fever in childhood and another episode after induction into the Army in 1941. He felt well until 1945 when he began to have attacks of substernal aching pain on exercise. During the

past 6 years he has had repeated hemoptysis, exertional dyspnea, and paroxysmal nocturnal dyspnea and orthopnea. For the past year he required nitroglycerin for his substernal pain.

Physical examination. The point of maximal impulse was in the fifth interspace 4 to 5 centimeters to the left of the midclavicular line. There was a harsh, low pitched, systolic basal murmur transmitted to the neck. Electrocardiograms showed left ventricular hypertrophy and chest roentgenograms and fluoroscopy showed left ventricular enlargement and a calcified aortic valve.

On November 22, 1953, a transventricular aortic valvulotomy was performed. A left pleural effusion was removed by thoracentesis 8 days postoperatively. The remainder of his convalescence was uneventful and he was discharged on the thirtieth postoperative day.

CASE 13. C.C.O., 33 year old male, was admitted to Wadsworth Veterans Administration Hospital with no history of rheumatic fever. He first knew of a cardiac murmur 11 years ago while in military service. Several months prior to admission he had had severe episodes of anginal pain.

Physical examination. Blood pressure was 98/70. The heart was moderately enlarged to the left. There was a harsh, systolic murmur over the entire precordium, heard best over the aortic area and transmitted into the neck. A soft, diastolic murmur was present along the left sternal border. Electrocardiograms showed left ventricular hypertrophy and roentgenograms showed slight left ventricular enlargement.

A diagnosis of aortic stenosis was made, and a transventricular aortic valvulotomy was performed on December 11, 1953. His postoperative course was uneventful. Since operation he has had no angina. He was discharged on the twenty-sixth postoperative day.

RESULTS

Thirteen patients were operated upon in this series. Six had relatively pure aortic stenosis and 2 had aortic stenosis and insufficiency. One had aortic stenosis and coarctation of the aorta, and 4 had aortic and mitral stenosis and mitral insufficiency. The stenoses of all these patients, except 1 who had congenital valvular disease, were thought to be the result of rheumatic heart disease. Age range was from 14 to 63 years, the majority being between 30 and 45 years. Follow-up studies of all cases lasted for at least 4 months, the longest being for 15 months. Objective evaluation is difficult, and patients, for the most part, have been evaluated subjectively. The disappearance of symptoms such as easy fatigability, palpitation, exertional dyspnea, and angina has been the chief criterion in judging the extent of benefit achieved.

The oldest patient, a man of 63, died during the operative procedure of irreversible cardiac arrest. A retrograde approach was attempted, employing a sternum splitting incision and entry through the innominate artery. When the valvulotome reached the region of the valve, cardiac arrest occurred. This was the only operative death in this series.

Two patients died approximately 9 and 3 months postoperatively. One was killed by severe traumatic cerebral injuries sustained in a barroom brawl. Another died of a pulmonary embolus and pulmonary congestion. This patient had both mitral and aortic stenosis and it was necessary to perform the mitral valvulotomy retrogradely through the ventricular incision with the aortic valvulotome because the left auricular appendage was extremely small and contracted. It was thought unwise to spend the time necessary to enter the auricle through the auricular wall or the pulmonary vein. Postmortem examination revealed that the left auricular appendage was filled with thrombus, severe pulmonary congestion, and a pulmonary embolus.

Nine of the patients had angina of varying degrees of severity. This symptom has been noted postoperatively in only 1 patient who had an unsatisfactory dilatation of the valve because of severe hemorrhage during operation. Exertional dyspnea was a prominent symptom in 12 patients and has been relieved in all but 2 of them. Fatigability was noted by all patients and was relieved in all but 2 of the 10 survivors. Exercise tolerance increased in all patients. Palpitation or heart consciousness was specifically noted by only 5 patients. Of these, 2 of 4 who survived still noticed palpitation. Three patients had a postoperative diastolic murmur which had not been heard before operation. All of these patients were considerably improved.

Of the 10 patients who survived more than 4 months, improvement was questionable in only 1, and we were not sure of the efficacy of valvulotomy because of hemorrhage at operation. The results of the others were considered from good to excellent. Pressure measurements made in the left ventricle and aorta

of several of the patients showed a fall in left ventricular pressure and a rise in aortic pressure.

In none of these patients has significant aortic insufficiency developed. A diastolic murmur of very soft intensity, however, has been noted in 3 patients after operation, but the peripheral blood pressure shows no evidence of insufficiency. The systolic murmur does not disappear but is usually much softer and less harsh. Occasionally it may be even louder than preoperatively.

DISCUSSION

The problems associated with aortic valvulotomy are considerably more complex than those encountered in treating mitral stenosis. A patient with aortic stenosis who is asymptomatic to any degree should be considered a candidate for operation because such a patient, unlike one with mitral stenosis, may die of intractable acute heart failure a relatively short time after onset of symptoms.

Bailey (2) has advocated the use of a retrograde approach on all patients with pure aortic stenosis. He accomplishes this procedure by suturing a pouch of plastic material to the wall of the aorta, and introducing both his finger and the dilating instrument into the aorta simultaneously. The dilating instrument is then guided into the valve by digital palpation. The retrograde approach employing digital palpation has the advantage over the ventricular approach of possibly offering more satisfactory control of bleeding. Also a wound is not made in the ventricular myocardium and, therefore, fewer serious arrythmias should be produced. With the palpating finger one can more accurately evaluate the pathologic lesion in terms of the degree of calcification and stenosis, and determine whether or not the valve has been opened satisfactorily. In addition one may determine if the valve is bicuspid or tricuspid, although when considerable calcification is present this is very difficult. Also, if a sternum splitting incision is used, neither pleural cavity is entered. This technique has the disadvantage of being tedious and time-consuming. Resuscitation in the event of cardiac arrest or ventricular fibrillation is far more difficult with either the sternum splitting or right anterior incision, and operations upon combined valvular lesions simultaneously are nearly impossible.

The ventricular approach, on the other hand, has the advantage of offering an easy entry through the left anterior fifth intercostal space. One can inspect the size and general configuration of the heart. Pressures in all chambers can be measured easily and resuscitative measures can be initiated if necessary. Dual lesions can also be treated simultaneously through a left thoracotomy incision. One of the greatest problems in using the transventricular approach is the control of bleeding from the hypertensive left ventricle. One would think that the thickness of such a ventricle would minimize bleeding as a potential hazard. However, occasionally such a ventricle is soft and spongy and does not hold sutures well. The purse-string suture should be of heavy material, such as No. 2 or 3 silk, and should be placed so that the bites are deep and have as much suture left between them as is buried, because the epicardium is the strongest part of the ventricular wall, and the suture will more than likely cut through the remaining ventricular muscle and pull out, if it cuts through the epicardium. This happened 3 times before we realized the importance of these principles in placing the purse string. Also, the dilator which we use is relatively small, the leading end being only $\frac{5}{16}$ inch in diameter (Fig. 5). The assistant should tighten the purse string only enough to prevent excessive bleeding, and additional control should be achieved by means of pressure with a small sponge on the myocardium at the point of entry into the ventricle. Another disadvantage of the ventricular approach is the wound produced in the myocardium and the imminent possibility of producing significant arrythmias, particularly ventricular fibrillation. Thus far, however, ventricular fibrillation has not occurred during any of our operations. The ventricular wound is undesirable, but if closed with small, interrupted sutures, should not be deleterious. The use of novocain injected into the myocardium aids greatly in preventing arrythmias during actual manipulation.

At present we prefer to use the ventricular approach because of the ease and speed with

which it can be executed, and because experience has enabled us to control bleeding more effectively. No trouble finding the valve opening with the dilator has been encountered, and therefore we have not felt the need for a guide wire.

Dual stenotic lesions present a compound problem, in that 2 valves have to be opened. White and Jones found that the incidence of aortic and mitral disease was twice that of aortic disease alone in a large series of patients with valvular heart disease. Some of our most satisfactory results have been achieved in patients with dual lesions who responded favorably to simultaneous valvulotomies. Originally we thought that the aortic valve should be opened initially because it would immediately increase the coronary artery blood flow, and because the mitral stenosis would prevent such a large blood flow into the left ventricle and aid in controlling bleeding from the ventricular wound. We now believe that the valve which seems to be most significantly affected should be opened first. For example, if the patient's primary symptoms have been angina and pounding, the aortic valve is opened first, whereas if primarily pulmonary edema and dyspnea are present, the mitral takes precedence. One should carefully evaluate patients with severe mitral stenosis who are thought to have only minimal aortic stenosis, because relieving the mitral stenosis will greatly accentuate what may seem to be minimal aortic stenosis. Several patients previously operated upon for mitral stenosis, with what was thought to be insignificant aortic stenosis, now have a loud aortic systolic murmur and symptoms of aortic stenosis.

In considering the complications which may arise, hemorrhage, ventricular fibrillation, and acute heart failure are all imminent at the time of operation. In the immediate postoperative period these must again be considered. An embolus, possibly from a calcified valve or from a thrombus in the ventricle or left auricle, is always a possibility. Reactivation of rheumatic fever may occur somewhat later. Heart failure may occur if the myocardial reserve is low. As to whether or not there will be recurrence of the stenosis, only time can tell. It does not seem likely that a heavily calcified valve would reunite. The tendency of the aortic valve to calcify, however, may cause subsequent stiffening and partial stenosis.

In all probability the operations presently used cannot be improved upon until a plastic procedure can be performed directly on the valve or a satisfactory prosthesis substituted.

SUMMARY

During the past few years both experimental and clinical studies have resulted in the development of a procedure for the treatment of aortic stenosis, which consists of dilating the stenosed valve ring with an instrument so that the valve will tear along the fused commissural lines or the weakest point, which may be through a valve cusp. Thirteen case histories in which aortic valvulotomies were performed are reported. There was 1 operative death in a 63 year old patient, who died while a retrograde approach through the innominate artery was being attempted. Selection of candidates for aortic valvulotomy, classification of patients with aortic stenosis, and contraindications to the operative procedure are presented. The surgical technique and problems encountered in treating this group of patients are discussed.

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STUDIES OF THE RESPONSE OF THE AUTONOMIC NERVOUS SYSTEM FOLLOWING COMBAT INJURY

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THIS study of the response of the autonomic nervous system of the battle casualty was part of a broad study of the systemic response to injury carried out by the Surgical Research Team of the United States Army on the Eastern Front in Korea during 1952 and 1953. It does not permit a complete description of the function of the autonomic nervous system following injury. Its purpose has been to evaluate the status of autonomic activity, primarily sympathetic activity, in the wounded man to the extent of determining whether there was autonomic hyperactivity, hypoactivity, or normal activity in the battle casualty at the time of resuscitation. It was hoped that the findings might explain some of the syndromes observed following injury and therapy.

METHODS

The approach to the problem was to measure the digital skin temperature, pulse volume, and finger flow, plethysmographically before and after peripheral nerve block. This approach was selected in the belief that it provided the most sensitive available indices of sympathetic activity. The pulse volume and flow were determined from the finger tip of the fifth finger and the skin temperature was measured at the base of the fifth finger.

These determinations were made before and after unilateral ulnar nerve block. The ulnar denervation at the elbow was accomplished by infiltration with 2 to 5 cubic centimeters of 1 per cent procaine hydrochloride. Two injections of procaine were necessary to obtain satisfactory ulnar paralysis in some of the patients.

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Two patients with posttraumatic hypertension were studied in detail. One of the patients received phentolamine and hexamethonium and the other sodium amytal during the studies.

Blood flow in the finger was measured by the venous occlusion method. From 5 to 10 separate determinations, with at least 30 second intervals between them, were made at each trial and the average results are reported. The average value was used in an attempt to be more precise since we noted, as has Burton, that the minute to minute flow is widely variable.

The records of pulse volume have been satisfactory but the finger flow determinations were not consistently obtainable on all patients because of apprehension and restlessness exhibited by certain of the casualties which resulted in frequent movements during the recordings. It is desirable to have the patient supine and for him to remain motionless during the recording.

Along with the determinations mentioned, clinical observations and historic data pertinent to each patient were tabulated. The temperature range of the room and the relative humidity were recorded during the study.

Each patient was lying on a litter which was placed on a litter-frame during the study. The upper extremities were supported by pillows at the level of the heart. Every effort was made to make these patients comfortable. In warm environmental temperatures they were covered only by a towel whereas in cooler environments they were covered from the axillae downward with one or two blankets, depending on the patient's desire; the warmth created by the blankets could have interfered to a variable extent with full reflex vasoconstriction.

TABLE I.—OBSERVATIONS ON 23 CASES

Case No.	Age	Type of injury	Extent of injury	Blood loss	Interval between injury and onset of study (hours)	Clinical signs and symptoms	Blood pressure range		Temp. range of room, degrees F.	Relative humidity	Pulse volumes in cu. mm./5 cu. cm. of part				Maximal increase in pulse volume on blocked side, per cent diff.	Finger flows in cu. mm./5 cu. cm. of part/min.				Maximal increase in finger flow on blocked side, per cent diff.
											Before nerve block		After nerve block			Before nerve block		After nerve block		
							Systolic	Diastolic			Right 5th fing.	Left 5th fing.	Right 5th fing.	Left 5th fing.		Right 5th fing.	Left 5th fing.	Right 5th fing.	Left 5th fing.	
1 (A)	22	Land mine	Traumatic amp. rt. foot; pen. wound left leg	Sl.	3¾	Skin cool; sl. pallor; mod. severe thirst; good pulse volume; very lucid	152 to 120	115 to 80	60 constant	85	1.00	1.30	4.55	1.30	355					
											Right ulnar block									
2 (A)	22	.45 cal. pistol	Perf. wound rt. flank and RUQ abd.—extraperitoneal	Sl.	2	Skin warm and normal pink; sl. thirst; good pulse volume; very lucid	140 to 120	90 to 80	76.3 to 78.1	—	1.60	1.40	11.0	1.25	588					
											Right ulnar block									
3 (JA)	19	Mortar fragments	Traumatic amp. of rt. and left feet; multiple pen. wounds of both thighs and buttocks	Sl.	3	Skin cool, sl. pallor; slight thirst; good pulse volume; very lucid	140 to 92	90 to 50	67.3 to 71.0	80	0.60	0.95	4.45	—	642					
											Right ulnar block									
4 (A)	21	M1 rifle	Avulsive wound of rt. lower thigh with fracture of rt. patella and distal end of rt. femur	Sl.	10	Skin warm; normal pink nailbeds; no thirst; good pulse volume; very lucid	192 to 150	114 to 90	73.4 to 76.1	70	1.40	1.35	2.70	2.10	92.8	787	713	918	737	16.5
											Right ulnar block									
5 (A)	22	45 cal. pistol	Perf. wound of left leg and tibia	Sl.	4½	Skin cool; normal pink skin; no thirst; good pulse volume; very lucid	130 to 120	80 to 78	73.5 to 72.9	63	0.55	0.90	0.55	8.85	884	—	106	—	1400	1277
											Left ulnar block									
6 (A)	18	Mortar fragments	Mult. pen. wounds of both legs; fracture of rt. ankle	Sl.	5	Skin cool and normal pink; sl. thirst; good pulse volume; very lucid	160 to 140	100 to 90	65.7 to 66.3	90	0.50	0.70	0.65	4.30	514					
											Left ulnar block									
7 (K)	27	Mortar fragments	Fracture of tarsals and metatarsals of left foot; pen. wound of left lower leg	Sl.	?	Skin warm; nailbeds pink; sl. thirst; good pulse volume; lethargic	156 to 140	90	87.4 to 85.5	—	2.35	1.40	2.25	3.0	114	794	781	862	2150	175
											Left ulnar block									
8 (K)	33	Mortar fragments	Pen. wound of left leg with comp. spiral fracture of lower ⅓ of femur; small laceration of anterior neck	Sl	4½	Skin warm; normal pink; slight thirst; good pulse volume; lucid	130 to 116	80 to 60	82.2 to 82.6	35	5.20	4.25	7.80	14.75	247	2660	4720	3170	4580	3 decrease
											Left ulnar block									

9 (F)	27	Mortar fragments	Perf. wound entering med. upper left thigh and emerging from left buttock	Sl.	3¾	Skin cool; normal pink color; no thirst; good pulse volume; slightly lethargic; pilorection over arms and shoulders	114 to 90	80 to 70	78.8 to 77.4	50	1.70	0.95	1.70	6.55	590	846	371	458	2720	633
											Left ulnar block									
10 (A)	21	Mortar fragments	Pen. wounds of rt. leg, rt. thigh, and rt. lateral neck	Sl.	4¾	Skin very warm; normal pink; no thirst; good pulse volume; very lucid	156 to 120	90 to 80	84.9 to 87.8	25	1.55	2.40	1.55	5.75	140	396	897	548	2500	179
											Left ulnar block									
11 (K)	25	Small arms fire	Pen. wound of abdomen RUQ resulting in: extensive laceration of rt. lobe of liver; perf. of asc. colon, duodenum, and ileum; laceration of 2 rt. lumbar veins; extensive soiling of peritoneal cavity and perf. of diaphragm on the right	Sl.	4½	Cool skin; marked flush of face and neck; moderate thirst; pulse rapid and thready; lethargic and restless; patient died on 1st postoperative day— 25 hrs. after completion of surgery	120 to 60	70 to 20	81.0 to 79.9	50	0.55	0.65	3.20	0.65	481					
											Right ulnar block									
12 (K)	22	Shell fragment	Perf. wound LLQ of abdomen with exit on buttock; comp. fracture of left mid ilium	Mod.	1¾	Cool skin; mod. pallor; no thirst; pulse volume poor; intermittently lethargic	130 to 80	80 to 40	75.6 to 75.8	80	3.65	1.60	4.80	1.55	31.5	117	118	395	411	238
											Right ulnar block									
13 (A)	22	Land mine	Traumatic amputation of left leg and rt. foot; pen. wound of left forearm and fractured phalanx of left 4th finger	Sl.	5⅗	Cool skin; normal pink nailbeds; mod. thirst; good pulse volume; alert and lucid	142 to 130	96 to 80	68.2 to 68.3	60	0.25	0.80	0.40	2.35	194	—	—	—	—	—
											Left ulnar block									
14 (K)	22	Mortar fragments	Large tangential soft tissue wound of left lateral thigh with much tissue destruction	Sl.	7	Very cool skin; nailbeds normal pink; no thirst; good pulse volume; moderately lethargic	130 to 120	90 to 80	73.8 to 72.0	65	0.35	0.35	0.35	6.55	1770	174	148	119	1055	613
											Left ulnar block									
15 (K)	21	Mortar fragments	Pen. wounds of rt. arm, rt. leg, back, and buttocks; small laceration of scalp	Sl.	4½	Cool skin; slightly pale nailbeds; mild thirst; good pulse volume; restless and apprehensive	156 to 80	100 to 46	74.7 to 75.2	58	0.50	—	7.25	—	1350					
											Right ulnar block									

(K) - Korean
(A) - American
(F) - Filipino
(JA) - Japanese-American

$$\text{Maximal percentage increase in pulse volume or flow} = \frac{\text{Value after nerve block minus control value}}{\text{Control value}} \times 100$$

Precision in pulse volume and flow values is not maintained beyond the second significant figure.

Pulse volumes are expressed in cubic millimeters per 5 cubic centimeters of part and finger flows in cubic millimeters per 5 cubic centimeters of part per minute.

TABLE I.—OBSERVATIONS ON 23 CASES (CONTINUED)

Case No.	Age	Type of injury	Extent of injury	Blood loss	Interval between injury and onset of study (hours)	Clinical signs and symptoms	Blood pressure range		Temp. range of room, degrees F.	Relative humidity	Pulse volumes in cu. mm./5 cu. cm. of part				Maximal increase in pulse volume on blocked side, per cent diff.	Finger flows in cu. mm./5 cu. cm. of part/min.				Maximal increase in finger flow on blocked side, per cent diff.
											Before nerve block		After nerve block			Before nerve block		After nerve block		
							Systolic	Diastolic			Right 5th fing.	Left 5th fing.	Right 5th fing.	Left 5th fing.		Right 5th fing.	Left 5th fing.	Right 5th fing.	Left 5th fing.	
16 (K)	30	Mortar fragments	Pen. wound of lower lateral left chest with probable intra-abdominal injury and perforation of left diaphragmatic leaf	Mod.	4	Cool skin; slight pallor of conjunctivae; sl. thirst; rapid, thready pulse, moderately lucid	100 to 80	70 to 60	71.2 to 72.7	68	—	0.80	—	6.0	650					
												Left ulnar block								
17 (K)	21	Gunshot wound	Perf. wound entering left flank; emerging ant. lower chest just to rt. of sternum; perf. of stomach and diaphragm	Sl.	10	Skin cool; nailbeds pink; mod. severe thirst; mod. good pulse volume; intermittently lethargic	118 to 102	84 to 80	76.5 to 75.9	55	1.55	0.90	1.05	2.55	183	349	653	393	1069	64
												Left ulnar block								
18 (A)	21	Artillery shell fragments	Perf. wounds of rt. and left thighs; fract. of right fibula	Sl.	5½	Skin cool; normal pink color; slight thirst; good pulse volume; intermittently lethargic	144 to 130	90 to 60	70.2 to 71.2	75	1.50	1.35	1.10	5.65	319	539	721	375	3630	390
												Left ulnar block								
19 (A)	22	Mortar fragments	Pen. wound of RUQ of abdomen	Sl.	7½	Skin warm; normal pink color; no thirst; good pulse volume; very lethargic	138 to 120	84 to 64	86.0 to 88.3	65	3.20	1.90	1.90	5.70	200	722	389	498	1050	170
												Left ulnar block								
20 (A)	21	Mortar fragments	Comp. fract. involving lower leg, with involvement of tibia, fibula, and tarsal bones; pen. small wds. of rt. arm	Sev.	5	Skin warm; mod. pale skin; slight thirst; rapid, thready, pulse; markedly lethargic	134 to 70	70 to 0	90.0 to 90.3	—	4.35	4.0	3.15	3.40	15 decrease	7 pints of whole blood post block				
												Left ulnar block								
21 (A)	23	Mortar fragments	Traumatic amp. rt. lower leg; multiple pen. wounds of left lower leg	None (Postop.)	20	Skin warm; normal pink; slight thirst; rapid pulse of good volume; alert and apprehensive	164 to 148	96 to 106	84.4 to 90.3	55	3.15	3.75	3.60	3.75	14	1610	2300	1300	1630	19.2 decrease
												Right ulnar block				After sodium amytal gr. 3¾				
													2.70	4.05				1080	2100	
22 (A)	24	Mortar fragments	Pen. wounds of left flank and left buttock	Sl.	6	Skin warm; normal pink color; sl. thirst; slow, full pulse; slightly lethargic	100 to 86	40 to 46	81.3 to 82.7	—	1.65	1.75	1.85	19.0	985	303	370	475	4120	1014
												Left ulnar block								
23 (A)	22	Mortar fragments	Perf. wounds rt. leg with much soft tissue destruction; comp. comm. fract. of tibia	Sl.	4	Skin warm; slight pallor; mod. thirst; good pulse volume; mod. lethargic	130 to 110	80 to 70	83.8	72	3.35	3.75	3.50	5.25	40	1520	3080	2440	2930	5 decrease
												Left ulnar block								

The plethysmograph consists of a low pressure, volume sensitive transducer and a sensitive multichannel amplifier recording system similar to that used in the Grass electroencephalograph. The construction of the Grass transducers permits the use of air as a transmitting medium. The transducers are equipped with precision-made injectors so that calibration may be accomplished by the injection of 5 to 10 cubic millimeters of air into the system. At maximal gain in the system a change in finger-tip volume of 1.0 cubic millimeter results in a deflection of the pen of 20 millimeters. Electrically the system amplifies approximately 1.5 million times (7).

The Grass finger oncometer consists of a light metal cylinder, closed at one end, and from which two small metal side tubes extend —one from the closed end of the cylinder and the other from the sidewall. Both of these outlet tubes connect with the inside of the chamber. The tube on the closed end of the cylinder was connected to a rubber tube leading to the pressure transducer. The tube on the side of the cylinder could be opened or closed at will so that pressure within the oncometer could be allowed to equilibrate with atmospheric pressure. The oncometer was applied to the finger with kal-kord[1] which could be molded around the finger and cuff and produce an airtight seal without constriction.

The skin temperatures were recorded with specially designed Grass thermal resistors which when applied to the skin resulted in a very rapid response to temperature; these measurements were recorded on the same instrument.

Material. A total of 23 patients were studied in this series. All of these patients were battle casualties and the interval of time elapsing from injury until the time of study varied from 1.3 to 20 hours, the average being 5.7 hours. As far as could be determined these patients were normal healthy males prior to injury. Their ages varied from 18 to 33 years with an average of 22.5 years.

The causes of injury were limited to artillery and mortar fragments (16 patients, 69.5 per cent), small arms fire (5 patients, 21.8 per cent), and land mine explosions (2 patients, 8.7 per cent). Of the 23 patients studied 13 or 56.6 per cent were Americans; 8 or 34.8 per cent were Koreans; 1 or 4.35 per cent Japanese-American; and 1 or 4.35 per cent Filipino.

[1]Kal-kord is a pliable, nonhardening, putty-like substance used for weather-stripping.

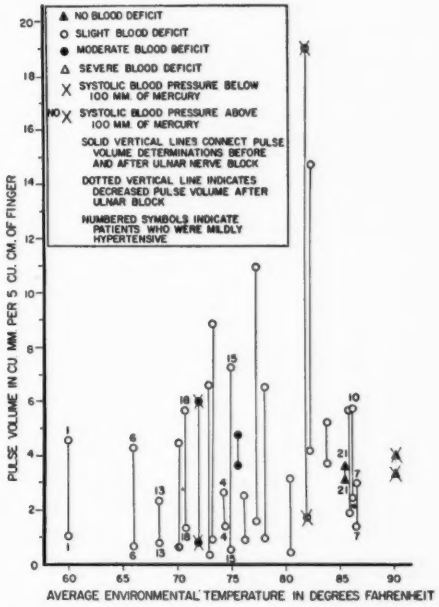

▲ NO BLOOD DEFICIT
○ SLIGHT BLOOD DEFICIT
● MODERATE BLOOD DEFICIT
△ SEVERE BLOOD DEFICIT
X SYSTOLIC BLOOD PRESSURE BELOW 100 MM. OF MERCURY
NO X SYSTOLIC BLOOD PRESSURE ABOVE 100 MM. OF MERCURY
SOLID VERTICAL LINES CONNECT PULSE VOLUME DETERMINATIONS BEFORE AND AFTER ULNAR NERVE BLOCK
DOTTED VERTICAL LINE INDICATES DECREASED PULSE VOLUME AFTER ULNAR BLOCK
NUMBERED SYMBOLS INDICATE PATIENTS WHO WERE MILDLY HYPERTENSIVE
PULSE VOLUME IN CU MM PER 5 CU. CM. OF FINGER
AVERAGE ENVIRONMENTAL TEMPERATURE IN DEGREES FAHRENHEIT

Fig. 1. Relationship between absolute values of pulse volume before and after ulnar nerve block and environmental temperature.

The significant clinical observations and values for the plethysmographic determinations made on each patient are categorized in Table I.

RELATIONSHIP BETWEEN INCREASE IN PULSE VOLUME AFTER ULNAR NERVE BLOCK AND ENVIRONMENTAL TEMPERATURE

The relationship between the environmental temperature and the absolute values for pulse volume before and after ulnar block in a given patient is demonstrated in Figure 1. Thus it reflects the degree of increase resulting from peripheral ulnar nerve block.

The relationship between the environmental temperature and the increase in pulse volume after ulnar block (expressed as per cent increase) is demonstrated in Figure 2. The solid

TABLE II.—RELATIONSHIP OF ENVIRONMENTAL TEMPERATURE AND BLOOD DEFICIT TO PULSE VOLUME BEFORE AND AFTER ULNAR NERVE BLOCK

Case No.	Average environmental temp. in degrees F.	Initial Absolute pulse volume before ulnar block in cu. mm./5 cu. cm. of finger	Absolute pulse volume after block in cu. mm./5 cu. cm. of finger	Percentage increase in pulse volume after block	Blood deficit	Morphine sulfate received prior to determination in mgm.
			60 to 70 degrees F.			
1	60.0	1.0	4.55	355	Slight	30
6	66.0	0.70	4.30	514	Slight	10
13	68.3	0.80	2.35	194	Slight	15
3	70.3	0.60	4.45	642	Slight	15
			70 to 75 degrees F.			
18	70.7	1.35	5.65	319	Slight	Dose?
16	71.9	0.80	6.0	650	Moderate	—
14	73.1	0.35	6.55	1770	Slight	30
5	73.2	0.90	8.85	884	Slight	—
4	74.3	1.40	2.70	92.8	Slight	15
15	74.9	0.50	7.25	1350	Slight	—
			75 to 80 degrees F.			
12	75.7	3.65	4.80	31.5	Moderate	—
17	76.2	0.90	2.55	183	Slight	—
2	77.3	1.60	11.0	588	Slight	—
9	78.1	0.95	6.55	590	Slight	Dose?
			80 to 85 degrees F.			
11	80.5	0.55	3.20	481	Slight	10
22	81.9	1.75	19.0	985	Slight	—
8	82.4	4.25	14.75	247	Slight	—
23	83.8	3.75	5.25	40	Slight	30
			85 to 90 degrees F.			
21	85.5	3.15	3.60	14	None	15
19	86.0	1.90	5.70	200	Slight	Dose?
10	86.2	2.40	5.75	140	Slight	—
7	86.5	1.40	3.0	114	Slight	10
20	90.1	4.0	3.40	15 (decrease)	Severe	15

black line on this graph indicates the average percentage increase in pulse volume values for all patients studied in the various ranges of environmental temperature.

These data are categorically recorded as to the various ranges of environmental temperature studied in Table II.

In the highest temperature ranges there is a tendency for the increases after block to be relatively small which would be expected since at these higher temperatures patients would tend to be in a state nearer to the maximal vasodilatation level. This observation seems to be the only correlation in the data between the values for increase in pulse volume after ulnar nerve block and the environmental temperature.

RELATIONSHIP BETWEEN INITIAL ABSOLUTE VALUES FOR PULSE VOLUME AND ENVIRONMENTAL TEMPERATURE

The relationship between the initial absolute values for pulse volume before ulnar nerve block and the environmental temperature is demonstrated in Figure 3. Between 72.5 and 82.5 degrees Fahrenheit there is a sudden marked increase in initial absolute pulse volume values with relatively smaller increases in environmental temperature. The solid black line indicates the average initial pulse volume values for all patients studied in a given range of environmental temperature.

On a physiologic basis it would appear logical to expect that higher ambient temperatures would result in release of vasomotor tone in the vessels supplying the skin of the finger tip with resulting vasodilatation and increase in pulse volume. From this graph one could possibly assume that the release of vasomotor tone in the skin vessels takes place rather rapidly between the temperatures of 72.5 and 82.5 degrees Fahrenheit.

This is the only definite correlation which we were able to establish from the data on this graph.

RELATIONSHIP BETWEEN THE ADMINISTRATION OF MORPHINE AND THE INITIAL ABSOLUTE VALUE FOR PULSE VOLUME

The dosages of morphine received by the patients with the values for the initial absolute pulse volumes prior to ulnar nerve block are tabulated in Table II in which the cases are arranged according to the range of environmental temperature. The information regarding the administration of morphine was obtained from the emergency medical tag which was the only medical record accompanying patients to the hospital from more forward medical installations.

Morphine, stated by Goodman and Gilman, even in therapeutic doses has been shown to cause dilatation of cutaneous vessels. However, if the initial absolute values for pulse volume before ulnar block are evaluated with regard to whether or not the patients received morphine, a correlation could not be established. If a correlation did exist, we would expect to find larger values for initial pulse volume in the group that received morphine. Fourteen or 61 per cent of the patients received morphine prior to study; the average initial absolute pulse volume value before ulnar block in this group was 1.55 cubic millimeters per 5 cubic centimeters of finger. The average of the environmental temperatures in which this group of patients was studied was 76.7 degrees Fahrenheit. Nine or 39 per cent of the patients received no morphine prior to study; the average initial absolute pulse volume value for this group was 1.85 cubic millimeters per 5 cubic centimeters of finger. The average of the environmental temperatures in which this group of patients was studied was 77.7 degrees Fahrenheit. There is no significant difference between these two groups.

RELATIONSHIP BETWEEN BLOOD DEFICIT AND PULSE VOLUME

The blood volume deficit was estimated clinically on the basis of extent of injury, the clinical observations on each patient, and the amount of blood required during resuscitation. Of the 23 patients studied, 1 or 4.35 per cent was considered to have no blood deficit because he was studied 11½ hours postoperatively, was adequately transfused, and was hypertensive (Case 23). Nineteen, or 82.6 per cent, were estimated to have slight blood deficit; 2, or 8.7 per cent, moderate blood deficit; and 1, or 4.35 per cent, severe blood deficit.

The average values for initial absolute pulse volume before block and for per cent increase after block are categorized, according to the degree of blood deficit, as follows:

In the 1 patient with no blood deficit the initial absolute pulse volume was 3.15 cubic millimeters per 5 cubic centimeters of finger, the increase after ulnar block 40 per cent; in the 19 patients with slight blood deficit the average initial absolute pulse volume was 1.40

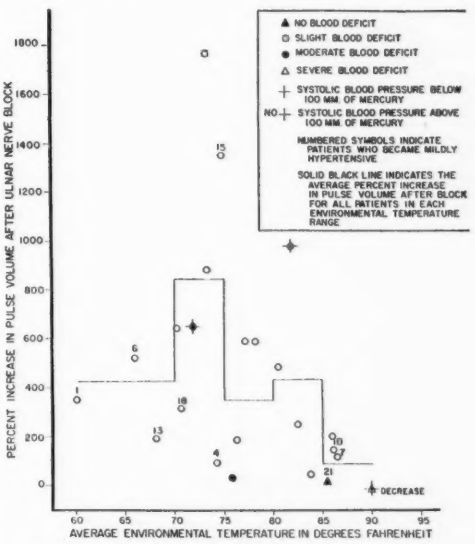
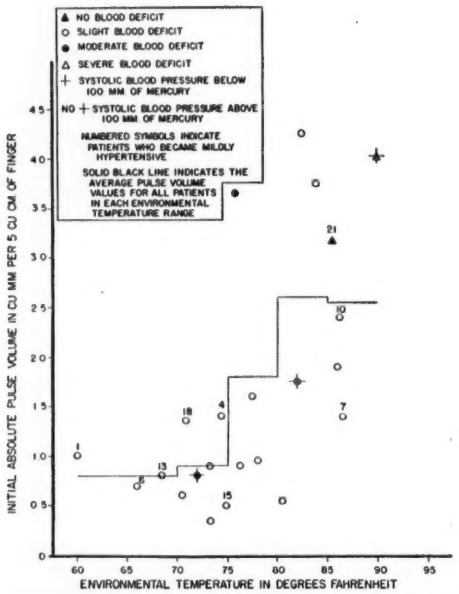


Fig. 2. Relationship between per cent increase in pulse volume after ulnar nerve block and the various ranges of environmental temperature in which patients were studied.

cubic millimeters per 5 cubic centimeters of finger, the average increase after block 509.9 per cent; in the 2 patients with moderate blood deficit the average initial absolute pulse volume was 2.25 cubic millimeters per 5 cubic centimeters of finger, the average increase after block 340.8 per cent; in the 1 patient with severe blood deficit the initial absolute pulse volume was 4 cubic millimeters per 5 cubic centimeters of finger, the decrease after block 15 per cent.

In this series the number of patients with slight blood deficit was much larger than any of the other groups categorized on the basis of blood deficit. Thus a definite correlation could not be established between the amount of blood deficit prior to the study and the initial absolute value of pulse volume. Likewise a definite correlation could not be established between the degree of blood deficit and the percentage increase in pulse volume after nerve block. However, it should be noted that those patients with systolic blood pressures of 140 or more millimeters of mercury, all of whom had slight or no blood loss, showed relatively small increases in pulse volume after block. This phenomenon is particularly strik-


NO BLOOD DEFICIT
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NUMBERED SYMBOLS INDICATE PATIENTS WHO BECAME MILDLY HYPERTENSIVE
SOLID BLACK LINE INDICATES THE AVERAGE PULSE VOLUME VALUES FOR ALL PATIENTS IN EACH ENVIRONMENTAL TEMPERATURE RANGE
INITIAL ABSOLUTE PULSE VOLUME IN CU MM PER 5 CU CM OF FINGER
ENVIRONMENTAL TEMPERATURE IN DEGREES FAHRENHEIT

Fig. 3. Relationship between the initial absolute values of pulse volume and the various ranges of environmental temperature in which patients were studied.

ing in Cases 7, 10, and 21 when the environmental temperature during the study was between 85.0 and 90.0 degrees Fahrenheit. This suggests that in this relatively hypertensive group of patients a humoral agent might have been producing vasoconstriction so that nerve block would not release the vasomotor tone.

It should also be noted that Case 20 with severe blood loss was studied at an environmental temperature of 90 degrees Fahrenheit and that the initial pulse volume was large. If reflex vasoconstriction occurs in shock, either this patient did not demonstrate the phenomenon, or the high environmental temperature overcame the effect.

RELATIONSHIP BETWEEN TYPE OF INJURY AND PULSE VOLUME

All of the patients were selected so that the significant wounds were either extremity or abdominal. Of the 23 patients studied 16 or 69 per cent had extremity wounds and 7 or 31 per cent had abdominal wounds. The values for initial absolute pulse volume and per cent increase in pulse volume after nerve block, according to the type of injury incurred, are categorized in Table III. There is no difference in the values for average initial absolute pulse volume or per cent increase in pulse volume after block between these two groups categorized on the basis of type of wound.

TABLE III.—RELATIONSHIP BETWEEN TYPE OF INJURY AND PULSE VOLUME

Case No.	Initial absolute pulse volume before ulnar block in cu. mm./5 cu. cm. of finger	Per cent increase in pulse volume after ulnar block
Abdominal Wounds		
2	1.60	588
11	0.55	481
12*	3.65	31.5
16*	0.80	650
17	0.90	183
19	1.90	200
22	1.75	985
Average	1.60	455.5
Extremity Wounds		
1	1.0	355
3	0.60	642
4	1.40	92.8
5	0.90	884
6	0.70	514
7	1.40	114
8	4.25	247
9	0.95	590
10	2.40	140
13	0.80	194
14	0.35	1770
15	0.50	1350
18	1.35	319
20*	4.0	15 (decrease)
21*	3.15	14
23	3.75	40
Average	1.55	453.2

*Cases 12 and 16 of the abdominal group both experienced moderate blood deficit. Case 20 of the extremity group experienced severe blood deficit. Case 21 was considered to have no blood deficit at the time of the determinations. All of the other cases had slight blood deficit.

RELATIONSHIP BETWEEN INITIAL ABSOLUTE PULSE VOLUME, INCREASE IN PULSE VOLUME AFTER BLOCK, AND SYSTOLIC BLOOD PRESSURE

The patients are grouped according to the level of systolic blood pressure during the

TABLE IV.—RELATIONSHIP BETWEEN PULSE VOLUME AND SYSTOLIC BLOOD PRESSURE

Case No.	Initial absolute pulse volume in cu. mm./5 cu. cm. of finger	Per cent increase in pulse volume after ulnar block
Systolic blood pressure below 100 mm. of mercury		
16	0.80 (at 72° F.)	650
20	4.0 (at 90° F.)	15 (decrease)
22	1.75 (at 82° F.)	985
Average	2.35	540
Systolic blood pressure above 100 mm. of mercury		
1*	1.0	355
2	1.60	588
3	0.60	642
4*	1.40	92.8
5	0.90	884
6*	0.70	514
7*	1.40	114
8	4.25	247
9	0.95	590
10*	2.40	140
11	0.55	481
12†	3.65	31.5
13*	0.80	194
14	0.35	1770
15*	0.50	1350
17	0.90	183
18*	1.35	319
19	1.90	200
21*	3.15	14
23	3.75	40
Average	1.60	437.5

*Those patients who at sometime before or during the study had some degree of systolic hypertension (140 or more mm. of mercury).
†Systolic blood pressure just 100 mm. of mercury at the time of the determination.

determinations in Table IV. Of the 23 patients studied, 20 or 87 per cent had systolic blood pressures above 100 millimeters of mercury; 3 or 13 per cent of the patients had systolic blood pressures below 100 millimeters of mercury. The average values for initial pulse volume before block and the per cent increase in pulse volume after block in the two groups also appear in Table IV.

The relationship between percentage increase in pulse volume following ulnar nerve block and the systolic blood pressure is demonstrated in Figure 4. Again it is emphasized that the patients in whom systolic blood pressure was 140 or more millimeters of mercury reacted with relatively small increases in pulse volume after peripheral ulnar nerve block.

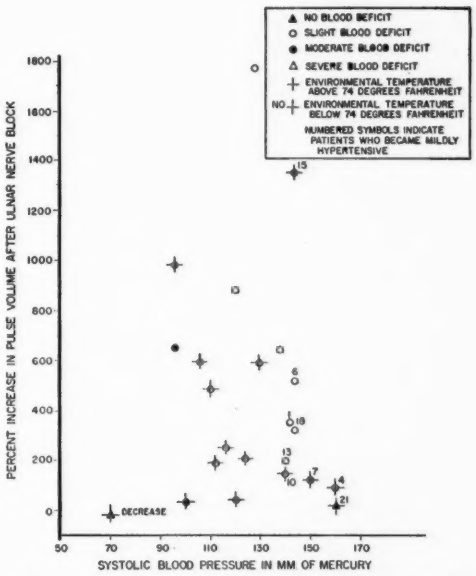

Fig. 4. Relationship between per cent increase in pulse volume after ulnar nerve block and systolic blood pressure.

The group of patients in whom systolic blood pressure fell below 100 millimeters of mercury is so very small in comparison to the group in whom systolic pressure remained above 100 millimeters that a correlation between pulse volume and systolic blood pressure is not justified.

Cases 12 and 16 both had moderate blood deficit; Case 20 had severe blood deficit. Cases 16 and 20 were both in the group in which systolic blood pressure was below 100 millimeters of mercury. Case 12 had a systolic blood pressure of just 100 millimeters of mercury at the time of the determination. Cases 12 and 20 were both studied at relatively high ambient temperatures.

Various types of blood pressure response were observed in this group of patients. The following categorizes the patients according to the type of systolic blood pressure[1] response:

[1]Patients who in the supine position had systolic blood pressures of 140 millimeters of mercury and above were considered to be hypertensive.

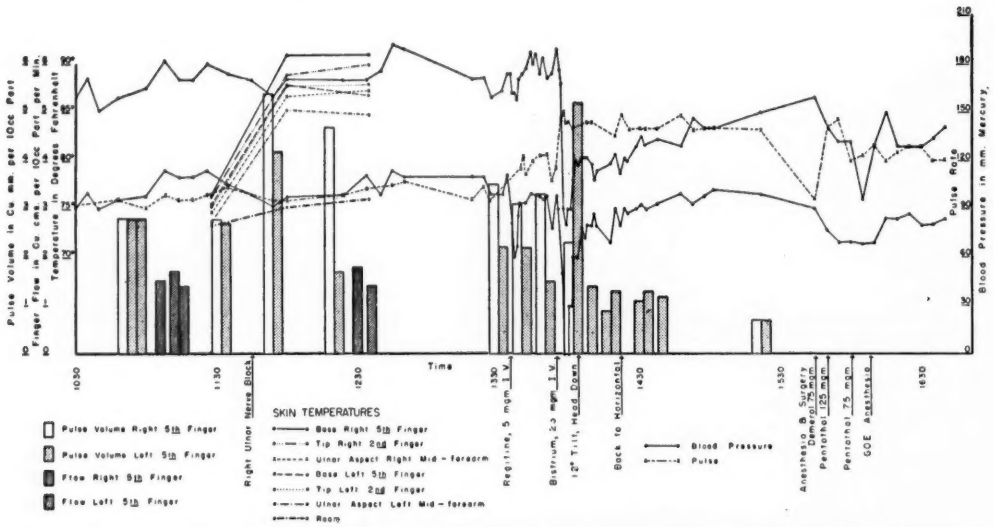

Fig. 5. Case 4. Graphic illustration of the response of a hypertensive battle casualty who was given phentolamine and hexamethonium bromide.

1. Patients who were normotensive from the onset of injury until the completion of our studies without blood or fluid replacement—Cases 2, 5, 8, 9, 14, 17, 19, 23.

2. Patients who were originally normotensive but became mildly hypertensive with fluid or blood replacement—Cases 1, 13.

3. Patients who were hypertensive from the onset of injury until completion of our studies without fluid or blood replacement—Cases 4, 6, 7, 10, 18.

4. Patients who were at first hypotensive but became hypertensive with blood and fluid replacement; our studies were made during the hypertensive period—Cases 15, 21.

5. Patient who was at first hypotensive but became normotensive with fluid or blood replacement—Case 11.

6. Patients who were hypotensive from the onset of injury until completion of our studies—Cases 12, 16, 20, 22.

POSTTRAUMATIC HYPERTENSION

Two of the patients in the hypertensive group (Table IV) were studied in detail. Each of these patients is reported here in detail with case summaries and charts depicting the results of the study.

CASE 4. A 21 year old colored male was shot just outside his company area with an M1 rifle at 2400 hours on May 10, 1953. He arrived at the battalion aid station at 0030 hours on May 11, 1953 where his wounds were cleaned and dressed and he received penicillin, tetanus toxoid, and 15 milligrams of morphine sulfate. He arrived at the clearing station at 0750 hours where he was again given 15 milligrams of morphine sulfate. He was then evacuated to the 46th Army Surgical Hospital by helicopter, arriving there at 1020 on May 11, 1953.

On admission he was found to have an evulsive wound of the right lower thigh with associated fracture of the right femur. The patient was hypertensive on admission and remained so throughout the entire period preceding surgery. His skin was warm; nailbeds were pink; pulse was of good volume; he complained of slight intermittent pain in the right thigh at the site of injury. His total blood loss was estimated to be no more than 200 to 300 cubic centimeters.

The interval of time elapsing between injury and the onset of our experimental procedure was approximately 10½ hours. The duration of the study was approximately 5 hours.

Following a right ulnar nerve block the maximal percentage increase in pulse volume bilaterally was 93 per cent. However, during this period of time the room temperature increased from 73.4 to 75.2 degrees Fahrenheit and the skin temperatures on both the blocked and unblocked sides increased 10 to 15 degrees in the interval of time from the control tracings until the tracings were repeated after ulnar nerve block. It is obvious from these findings that the patient was in the process of stabilization in the presence of a somewhat changing environmental temperature. Consequently it is impossible to evaluate what portion of the increase in pulse volume and skin temperature on the right side could be at-

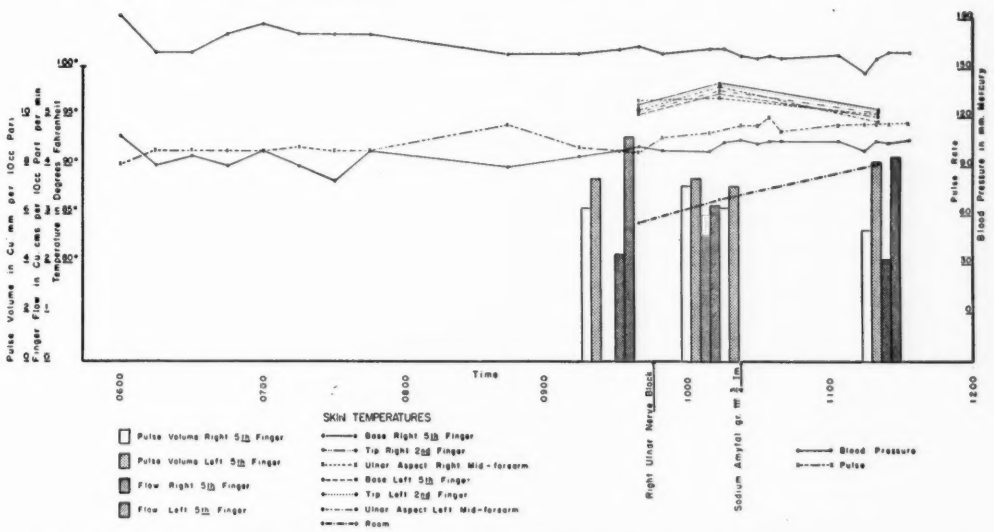

Fig. 6. Case 21. Graphic illustration of the response of a hypertensive battle casualty who was given sodium amytal.

tributed to the right ulnar nerve block; the evaluation would be impossible because of the many variables involved.

At one point in the procedure 5 milligrams of phentolamine were given intravenously. There was no appreciable change in the pulse volume on either the right or left sides after the administration of this drug. There was a slight transient drop in the diastolic blood pressure but little change in the systolic pressure.

At another point in the procedure 25 milligrams of hexamethonium bromide were given intravenously at a rapid rate. The administration of this drug resulted in a maximal percentage increase in pulse volume in the left fifth finger of 24 per cent. There was an associated abrupt fall in both systolic and diastolic blood pressure (190/98 to 90/0) and an increase in pulse rate from 116 to 150 per minute. The patient complained of vertigo and it was necessary to tilt him head-down for a few minutes. The increase in digital pulse volume produced by this drug was very transient. The markedly hypotensive effects lasted for about 5 minutes, and then, both systolic and diastolic pressures climbed gradually to the premedication level over a period of about 13 to 15 minutes.

During the experimental procedure the patient was covered with 1 wool blanket from the chest to his feet. After the administration of phentolamine and hexamethonium bromide blood pressures were taken at minute intervals by the cuff method on the right arm. The mechanics of the inflation of the blood pressure cuff tends to invalidate all plethysmographic determinations recorded from the right side because of the intermittent interruption of blood flow.

During anesthesia with pentothal the patient experienced another episode of hypotension. This tends to substantiate the thoughts of others who maintain that pentothal is a sympathetic ganglionic depressent agent. In this case there was similarity between the response to a known ganglionic blocking agent, hexamethonium, and the response to pentothal. The hypotensive phase occurring simultaneously with pentothal administration subsided only when the anesthetic agent was changed to gas, oxygen, and ether. The duration of anesthesia and surgery was approximately 1 hour, 45 minutes.

The accompanying graph in Figure 5 depicts the results of the determinations.

CASE 21. A 23 year old colored male was injured by mortar fragments on July 18, 1953 at approximately 1330 hours. Blood pressure recorded at the battalion aid station was 50/40. He received 200 cubic centimeters of serum albumin and 1,000 cubic centimeters of dextran in addition to 15 milligrams of morphine sulfate at the aid station. The patient was evacuated by helicopter and arrived at the 46th Army Surgical Hospital at approximately 1600 hours on July 18, 1953.

Examination at the hospital revealed a traumatic amputation of the right lower leg and multiple large penetrating wounds of the left lower leg and small penetrating wounds of the right arm. Blood pressure was 70/30 and pulse 144 per minute. Preoperatively the patient received 3,000 cubic centimeters of whole blood. At 1940 hours he was taken to surgery at which time both legs were amputated just below the

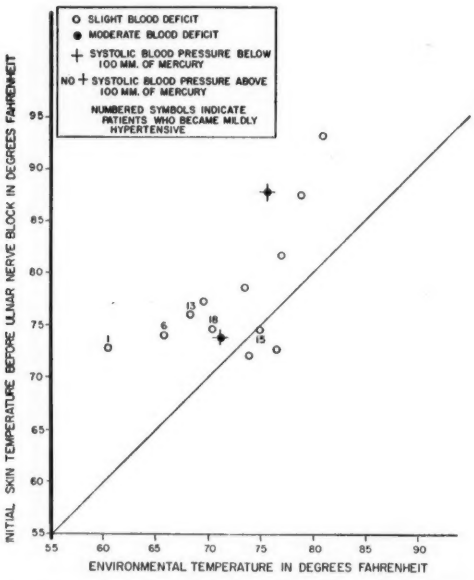

Fig. 7. Relationship between skin temperature before ulnar nerve block and environmental temperature.

knee joint. Surgery ended at 2140 hours; the patient received 2,500 cubic centimeters of whole blood during the surgical procedure.

Prior to surgery blood pressure ranged from 70 to 138 systolic and from 30 to 80 diastolic. Following surgery the patient's blood pressure began to rise gradually to reach hypertensive levels; at the eighth postoperative hour his blood pressure was 184/108. The studies were begun at approximately 11½ hours following the completion of surgery at which time the blood pressure was 164/102. At the time of the study the patient was moderately apprehensive and emotional about the loss of his legs. His skin was warm to palpation; color was normal; he was perspiring profusely; and the pulse was rapid and full.

Pulse volumes and finger flows were recorded bilaterally from the tips of the fifth finger. Initial values on the right and left fingers for pulse volume were 3.20 and 3.75 cubic millimeters per 5 cubic centimeters of finger, respectively. The values following right ulnar nerve block were 3.60 and 3.75 cubic millimeters per 5 cubic centimeters of finger, respectively. The slight increase on the right following right ulnar nerve block is insignificant. Following the nerve block there was complete anesthesia over the sensory distribution of the ulnar nerve in the hand. Finger flows actually decreased bilaterally after nerve block without any appreciable decrease in the blood pressure or pulse pressure.

Following this first part of the study the patient was given 225 milligrams of sodium amytal intramuscularly. The patient became quite lethargic and began to sleep soundly. There was only slight decrease in systolic pressure (14 mm. of mercury) over the period of an hour following the administration of sodium amytal and then the pressure returned gradually to its original level. Pulse volumes at this time showed no appreciable consistent change as a result of sodium amytal sedation.

The environmental temperature during this study ranged from 84.4 to 90.3 degrees Fahrenheit. These studies reveal that this man, even though hypertensive, did not show evidence of vasoconstriction in the skin and subcutaneous tissue as measured in the finger tip but, rather, was initially relatively vasodilated as one would expect a normal man to be in a very warm environment. Certainly if this patient had arteriolar constriction contributing to his hypertension it was not apparent in the skin and subcutaneous tissue of the finger tips.

The accompanying chart in Figure 6 depicts the results of the significant determinations during this study.

RELATIONSHIP BETWEEN INITIAL SKIN TEMPERATURE PRIOR TO ULNAR BLOCK AND ENVIRONMENTAL TEMPERATURE

Fourteen of the 23 patients studied were considered to have skin temperature responses which were satisfactory for analysis. The initial skin temperatures at the base of the fifth finger on the side studied are plotted against the environmental temperature at the time in Figure 7. It will be observed that any point on the solid diagonal line represents a skin and an environmental temperature of the same magnitude. This line describes the behavior of the skin temperature under conditions of changing environmental temperature of a tissue which would theoretically be devoid of circulation, i.e., the skin temperature would be the same as that of the environment if sufficient time elapsed for equilibrium to be established. From this graph it will be seen that 11 of the 14 patients had initial skin temperatures which were above this line and indicating that the skin was warmer than the environment at the time of the determination. Three of the 14 patients (Cases 14, 15, and 17) had skin temperatures slightly less than the environmental temperature. This could result only from perspiration and cooling due to evaporation from the skin surface or, possibly, from the fact that the patient was brought from a cool to a warm environment and had not reached equilibrium with the new environ-

TABLE V.—RELATIONSHIP BETWEEN SKIN TEMPERATURE AND ENVIRONMENTAL TEMPERATURE

Case No.	Environmental temperature	Skin temperature prior to block at base of 5th finger	Skin temperature after ulnar block	Blood deficit	Systolic blood pressure at time of determination
1	60.3	72.6	82.6	Slight	132
2	77.0	81.7	85.5	Slight	130
3	69.6	77.2	93.7	Slight	128
5	73.5	78.5	100.2	Slight	120
6	65.7	73.8	81.8	Slight	150
9	78.8	87.3	97.2	Slight	110
11	81.0	93.1	95.8	Slight	114
12	75.6	87.6	89.1	Moderate	96
13	68.2	75.8	84.6	Slight	142
14	73.8	71.9	89.5	Slight	120
15	74.7	74.5	82.0	Slight	140
16	71.2	73.8	93.6	Moderate	98
17	76.5	72.5	79.3	Slight	118
18	70.2	74.6	94.6	Slight	140

All temperatures in degrees Fahrenheit.

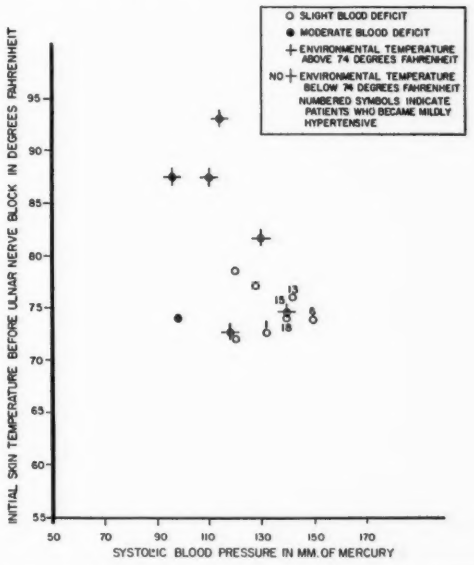

Fig. 8. Relationship between skin temperature before ulnar nerve block and systolic blood pressure.

ment. Cooling of the skin surface by evaporation or perspiration would tend to suggest that there was some degree of hyperactivity of the sympathetic nervous system. However, only 3 of the 14 patients demonstrated the phenomenon, all of which were considered to be in a state of slight blood deficit with systolic blood pressure above 100 millimeters of mercury at the time of the skin temperature determination. One of these 3 patients became mildly hypertensive during the study.

The values depicted in Figure 7 are found in the data recorded in Table V.

RELATIONSHIP BETWEEN INITIAL SKIN TEMPERATURE PRIOR TO ULNAR NERVE BLOCK AND SYSTOLIC BLOOD PRESSURE

The initial values for skin temperature before ulnar block are plotted against the systolic blood pressure at the time of the temperature determination in Figure 8. Only 2 of the 14 patients had systolic blood pressures which were below 100 millimeters of mercury at the time of the determination (Cases 12 and 16). Both of these patients were considered to be in a state of moderate blood loss. The other 12 patients had slight blood deficit and all had systolic blood pressures over 100 millimeters of mercury.

The graph in Figure 8 would indicate that there was a tendency for the patients with the highest systolic blood pressures to have the lower values for initial skin temperature before ulnar nerve block. Perhaps this indicates that there is some excessive degree of vasoconstriction in the vessels of the finger tip in this somewhat hypertensive group of patients.

RELATIONSHIP BETWEEN INCREASE IN SKIN TEMPERATURE AFTER ULNAR BLOCK AND ENVIRONMENTAL TEMPERATURE

The values for skin temperature at the base of the fifth finger before and after ulnar nerve block are plotted against the environmental temperature in Figure 9. The vertical lines connect the determinations before and after block in a given patient and thus indicate the increase in temperature resulting from sympathetic paralysis. There is a tendency for those cases which were studied at higher environmental temperatures to show smaller increases in skin temperature after ulnar

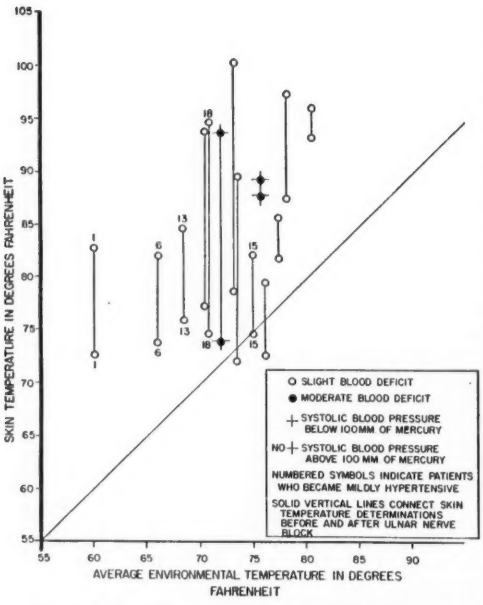
SKIN TEMPERATURE IN DEGREES FAHRENHEIT
AVERAGE ENVIRONMENTAL TEMPERATURE IN DEGREES FAHRENHEIT
O SLIGHT BLOOD DEFICIT
● MODERATE BLOOD DEFICIT
+ SYSTOLIC BLOOD PRESSURE BELOW 100MM OF MERCURY
NO + SYSTOLIC BLOOD PRESSURE ABOVE 100 MM OF MERCURY
NUMBERED SYMBOLS INDICATE PATIENTS WHO BECAME MILDLY HYPERTENSIVE
SOLID VERTICAL LINES CONNECT SKIN TEMPERATURE DETERMINATIONS BEFORE AND AFTER ULNAR NERVE BLOCK

Fig. 9. Relationship between skin temperature before and after ulnar nerve block and environmental temperature.

block. Three exceptions to this observation were Cases 1, 6, and 13 which were studied in a range of environmental temperature from 60 to 70 degrees Fahrenheit. All 3 of these patients showed small increases after ulnar block and all had systolic blood pressures of 140 or more millimeters of mercury. These same 3 patients revealed relatively small increases in pulse volume after block. A possible explanation for the relatively small temperature and small pulse volume increases after sympathetic paralysis is that a circulating vasopressor substance could have maintained these peripheral vessels in a state of relative vasoconstriction following temporary denervation of the blood vessels.

DISCUSSION

In the normal human it has been shown by Morton and Scott that the normal maximal vasodilatation level for skin temperature after sympathectomy, procaine nerve block, or spinal anesthesia is approximately 95 degrees Fahrenheit. If it is assumed that the patients in this series had normal blood vessels and that satisfactory peripheral ulnar nerve blocks were obtained, the attainment of maximal vasodilatation would indicate that the patient had a normal blood volume and normal cardiac output. All of these patients had complete anesthesia in the skin of the hand innervated by the ulnar nerve following ulnar nerve block; thus, the belief was that the blocks were successful. Failure to obtain maximal vasodilatation in the vessels of the fifth finger after sympathetic paralysis indicates that there was a deficit of blood reaching the finger tip which could be due to oligemia and decreased cardiac output. Thus the degree to which these patients failed to reach the maximal vasodilatation level (95 degrees Fahrenheit) after sympathetic paralysis should reflect the degree of oligemia and decreased cardiac output unless circulating vasopressor substances were responsible for vasoconstriction in these vessels. The degree to which the skin temperature at the base of the fifth finger failed to reach the maximal vasodilatation level is expressed by the ratio of experimental value for skin temperature after ulnar nerve block/theoretic maximal value (95 degrees Fahrenheit) in Figures 10 and 11. The solid black horizontal line represents a ratio of 0.95 or a skin temperature of approximately 90 degrees Fahrenheit. Thus it is assumed, for purposes of discussion, that in the cases with ratios of 0.95 to 1.00 (skin temperatures of 90 to 95 degrees Fahrenheit after ulnar nerve block) maximal vasodilatation had occurred. Thus all the ratios which were below this line represent patients in whom maximal vasodilatation was not present after ulnar nerve block. The relationship between this ratio and the environmental temperature is demonstrated in Figure 10. The relationship between this ratio and the systolic blood pressure is demonstrated in Figure 11. The data for these graphs are presented in Table VI.

Of the 14 patients in whom skin temperature response was evaluated, 8 or 57 per cent of the patients failed to reach the maximal vasodilatation level after ulnar block. Only 1 of these patients (Case 12) suffered moderate blood deficit; all of the remaining 7 patients had only slight blood deficit at the time of the

determination. Four of these 8 patients had systolic blood pressures which were considered to be hypertensive at the time of the determination (Cases 1, 6, 13, and 15). In this hypertensive group, in which blood deficit was only slight, a circulating vasopressor substance could possibly be responsible for their failure to reach the maximal vasodilatation level following paralysis of the sympathetic supply to the vessels in the fifth finger tip; this of course, is only speculation.

There were 3 other cases with slight blood loss which failed to reach the maximal vasodilatation level after sympathetic block (Cases 2, 14, and 17). All of these 3 patients were normotensive on admission to the hospital and remained normotensive through the completion of the studies without fluid or blood replacement. There is no apparent explanation for their failure to reach the maximal vasodilatation level unless it be an expression of oligemia.

A correlation could not be established between the environmental temperature and whether or not patients reached the maximal vasodilatation level.

At present it is not possible to express definitely whether or not a given patient is vasoconstricted from observation of the absolute value of pulse volume. The range of pulse volume values at varying degrees of environmental temperature is unknown. It is conceivable that the range of values at any given temperature might be quite wide. Thus it is a decided disadvantage not to have baseline values with which to compare the patients in this series. Consequently there were limitations in the selection of a yardstick by which autonomic activity could be evaluated in these patients. Since the initial absolute value for pulse volume is somewhat of a variable, the degree of increase after sympathetic paralysis was chosen as a measure of autonomic activity. This is open to criticism because it must be assumed that a given degree of oligemia or a certain deficit of cardiac output will have the same relative effect on the rate of blood flow during vasoconstriction as during vasodilatation. There is no evidence at present upon which to base this assumption. Although the increase in pulse volume and

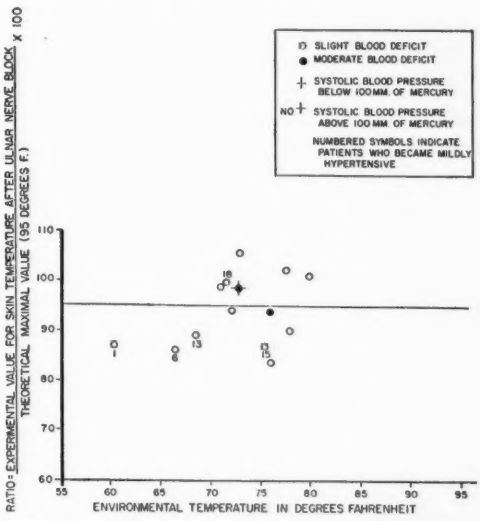

Fig. 10. Relationship between the ratio of experimental value of skin temperature after ulnar nerve block/theoretic maximal value and environmental temperature.

skin temperature resulting from sympathetic paralysis is a measure of sympathetic activity in a given pateint, 1 patient would not be comparable to another if there were great variability between patients in the degree of blood volume deficit. In this series of 23 patients, however, it was estimated clinically that 19 were in a state of slight blood deficit and 1 had no blood deficit; of the 3 remaining patients, 2 were in a state of moderate blood deficit and 1 in a state of severe blood deficit. It appears that difference in degree of oligemia was not a significant factor in most of these patients and the degree of increase in pulse volume and skin temperature after ulnar block should be a reasonably satisfactory approximation of vasomotor activity. The initial vasomotor activity as manifested by increase in pulse volume and skin temperature after sympathetic paralysis would also be a function of the initial environmental temperature.

The maximal vasodilatation level for pulse volume is not definitely established. An attempt was made to establish a theoretic maximal value from pulse volume studies, obtained by Simeone and associates (6), on 33 patients with normal circulation. These pulse volume studies had been made from the fifth

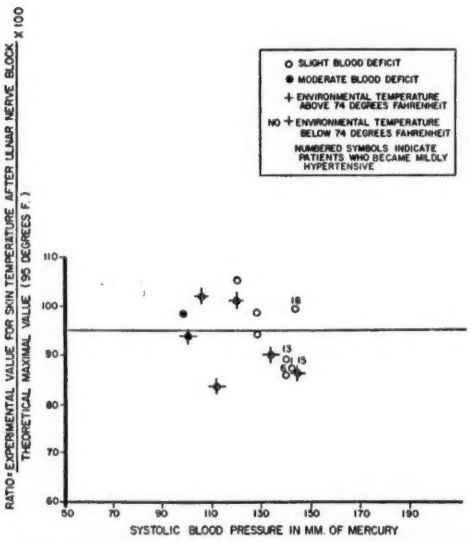
RATIO: EXPERIMENTAL VALUE FOR SKIN TEMPERATURE AFTER ULNAR NERVE BLOCK / THEORETICAL MAXIMAL VALUE (95 DEGREES F.) X 100
O SLIGHT BLOOD DEFICIT
● MODERATE BLOOD DEFICIT
+ ENVIRONMENTAL TEMPERATURE ABOVE 74 DEGREES FAHRENHEIT
NO + ENVIRONMENTAL TEMPERATURE BELOW 74 DEGREES FAHRENHEIT
NUMBERED SYMBOLS INDICATE PATIENTS WHO BECAME MILDLY HYPERTENSIVE
110
100
90
80
70
60
50 70 90 110 130 150 170 190
SYSTOLIC BLOOD PRESSURE IN MM. OF MERCURY

Fig. 11. Relationship between the ratio of experimental value of skin temperature after ulnar nerve block/theoretic maximal value and the environmental temperature.

TABLE VI.—RELATIONSHIP OF SKIN TEMPERATURE AFTER BLOCK TO THEORETIC MAXIMAL

Case No.	Skin temp. after ulnar block in degrees F.	Ratio = experimental skin temp. after ulnar block/theoretical maximal (95°)	Systolic blood pressure in mm. of mercury	Blood deficit	Environmental temp.
1	82.6	87	142*	Slight	60.1
2	85.5	90	134	Slight	77.9
3	93.7	98.6	128	Slight	71.0
5	100.2	105.4	120	Slight	72.9
6	81.8	86.1	140*	Slight	66.3
9	97.2	102	106	Slight	77.4
11	95.8	101	120	Slight	79.9
12	89.1	93.8	100	Moderate	75.8
13	84.6	89.0	140*	Slight	68.3
14	89.5	94.2	128	Slight	72.0
15	82.0	86.3	144*	Slight	75.2
16	93.6	98.5	98	Moderate	72.7
17	79.3	83.5	112	Slight	75.9
18	94.6	99.6	144*	Slight	71.2

*Indicates those patients who became hypertensive (systolic pressure 140 or more millimeters of mercury) prior to or during the determinations.

finger on normal upper extremities after ulnar nerve block. It was found that the pulse volume values for these 33 patients, who were maximally vasodilated, were extremely variable. However, as suggested by one of us (F.A.S.), 10 cubic millimeters per 5 cubic centimeters of finger have been used as the approximate theoretic maximal value for pulse volume after sympathetic paralysis.

The degree to which pulse volume failed to reach the maximal vasodilatation level is expressed by the ratio of experimental value for pulse volume after ulnar nerve block/theoretic maximal value (10 cu. mm./5 cu. cm. of part) in Figures 12 and 13. The solid black line on these graphs represents a ratio of 1.00. The relationship between this ratio and the environmental temperature is demonstrated in Figure 12. The relationship between this ratio and the systolic blood pressure is demonstrated in Figure 13. Data from all 23 patients, relative to these graphs, are in Table VII.

All but 3 of the patients failed to reach the maximal vasodilatation level for pulse volume. The existence of a deficit by which patients failed to reach the maximal vasodilatation level even at high environmental temperatures indicates that the deficit is not due to unsatisfactory peripheral ulnar nerve blocks. Therefore, the deficit would indicate that these patients either had oligemia and decreased cardiac output or had a humoral vasopressor substance in their circulation. Unfortunately, the effects of oligemia per se could not be separated from the possible effects of humoral agents. It seems most likely that a humoral vasopressor substance was operating to prevent large increases in pulse volume after ulnar block and to produce failure to reach the maximal vasodilatation level in the 9 hypertensive patients. Since regitine® had very little effect when used in Case 4, it is suggestive, as Emlet and Meier and their associates have pointed out, that if a humoral vasopressor agent was active, it was probably not adrenaline or noradrenaline.

The large degree by which most of these patients failed to reach the maximal vasodilatation level for both skin temperature and pulse volume after sympathetic paralysis would indicate that this deficit was not attributable to overactivity of the sympathetic

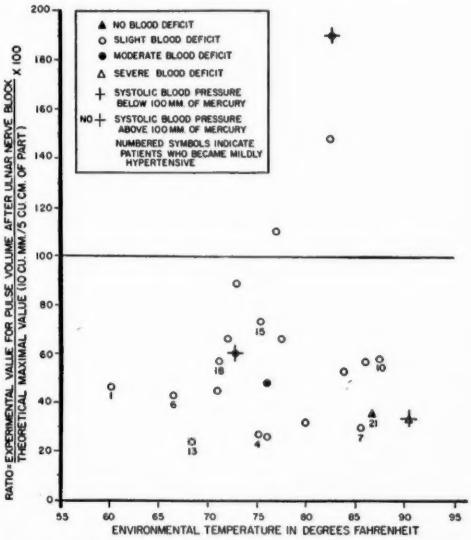
▲ NO BLOOD DEFICIT
○ SLIGHT BLOOD DEFICIT
● MODERATE BLOOD DEFICIT
△ SEVERE BLOOD DEFICIT
+ SYSTOLIC BLOOD PRESSURE BELOW 100 MM. OF MERCURY
NO + SYSTOLIC BLOOD PRESSURE ABOVE 100 MM. OF MERCURY
NUMBERED SYMBOLS INDICATE PATIENTS WHO BECAME MILDLY HYPERTENSIVE
RATIO = EXPERIMENTAL VALUE FOR PULSE VOLUME AFTER ULNAR NERVE BLOCK / THEORETICAL MAXIMAL VALUE (10 CU. MM./5 CU. CM. OF PART) X 100
ENVIRONMENTAL TEMPERATURE IN DEGREES FAHRENHEIT

Fig. 12. Relationship between the ratio of experimental value of pulse volume after ulnar nerve block/theoretic maximal value and the environmental temperature.

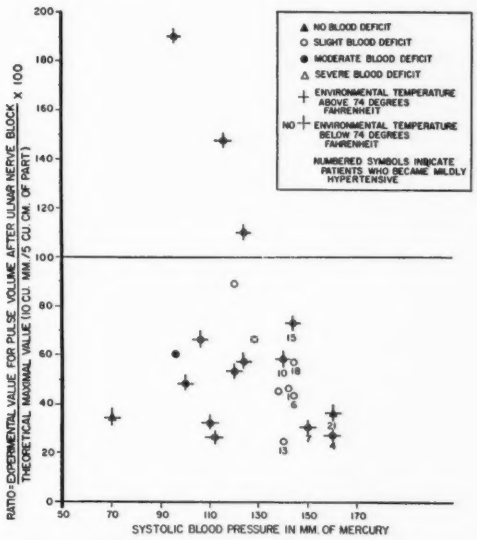
▲ NO BLOOD DEFICIT
○ SLIGHT BLOOD DEFICIT
● MODERATE BLOOD DEFICIT
△ SEVERE BLOOD DEFICIT
+ ENVIRONMENTAL TEMPERATURE ABOVE 74 DEGREES FAHRENHEIT
NO + ENVIRONMENTAL TEMPERATURE BELOW 74 DEGREES FAHRENHEIT
NUMBERED SYMBOLS INDICATE PATIENTS WHO BECAME MILDLY HYPERTENSIVE
RATIO = EXPERIMENTAL VALUE FOR PULSE VOLUME AFTER ULNAR NERVE BLOCK / THEORETICAL MAXIMAL VALUE (10 CU. MM./5 CU. CM. OF PART) X 100
SYSTOLIC BLOOD PRESSURE IN MM. OF MERCURY

Fig. 13. Relationship between the ratio of experimental value of pulse volume after ulnar nerve block/theoretic maximal value and the systolic blood pressure.

nerves per se but, rather, suggests that oligemia and decreased cardiac output or humoral vasoconstrictors were more important factors. The peripheral pallor seen in injured patients cannot be attributed entirely to exaggerated nervous activity. It has also been observed in Figure 9 that all but 3 of the 14 patients in whom skin temperatures were evaluated had an initial skin temperature greater than that of the environment. This finding would tend to indicate that there was no extraordinary overactivity of the sympathetic nerves.

From this study it can definitely be concluded that the sympathetic nervous system was functionally active in these patients and that sympathetic activity was not obliterated by the traumatic and circulatory insults experienced. However, the degree of activity in effect, i.e., normal activity, hypoactivity, or hyperactivity, could not be determined.

It must be realized that facilities did not exist in the field whereby environmental temperature and relative humidity could be controlled at a constant level during the period of study. However, should a constant temperature environment have been available, its proper utilization would have been impractical because of the short interval of time allowed for study on a wounded casualty prior to definitive surgery; a patient must be allowed to stabilize in a constant temperature environment for an hour or more before the constant temperature environment can be considered as a valuable control. When attempting to perform acute studies this is fraught with difficulties because of changes which could possibly occur in the individual as a result of the long period of stabilization.

From a hemodynamic point of view it must be remembered that these plethysmographic studies reveal only changes in blood flow and pulse volume in the skin and subcutaneous tissue of the finger tip. These must not be misconstrued to be representative of flow or flow changes which might have been present in other vascular beds such as muscular, splanchnic, coronary, or pulmonary. The circulatory changes which occurred in these other vascular areas may have been quite different and independent from those occurring in skin and subcutaneous tissue of the finger tip.

TABLE VII.—RELATIONSHIP OF PULSE VOLUME AFTER BLOCK TO THEORETIC MAXIMAL

Case No.	Pulse volume after block in cu. mm. per 5 cu. cm. of finger	Ratio=pulse volume after block/theoretic maximal (10 cu. mm. per 5 cu. cm. of finger)	Systolic blood pressure	Blood deficit	Environmental temperature at time of pulse volume determination
1	4.55	0.46	142*	Slight	60.1
2	11.0	1.1	124	Slight	77.7
3	4.45	0.45	138	Slight	71.0
4	2.70	0.27	160*	Slight	75.2
5	8.85	0.89	120	Slight	72.9
6	4.30	0.43	144*	Slight	66.3
7	3.0	0.30	150*	Slight	85.5
8	14.75	1.48	116	Slight	82.6
9	6.55	0.66	106	Slight	77.4
10	5.75	0.58	140*	Slight	87.4
11	3.20	0.32	110	Slight	79.9
12	4.80	0.48	100	Moderate	75.8
13	2.35	0.24	140*	Slight	68.3
14	6.55	0.66	128	Slight	72.0
15	7.25	0.73	144*	Slight	75.2
16	6.0	0.60	96	Moderate	72.7
17	2.55	0.26	112	Slight	75.9
18	5.65	0.57	144*	Slight	71.2
19	5.70	0.57	124	Slight	86.0
20	3.40	0.34	70	Severe	90.3
21	3.60	0.36	160*	None	86.7
22	19.0	1.9	96	Slight	82.7
23	5.25	0.53	120	Slight	83.8

*Indicates patients who became hypertensive (systolic pressure 140 or more millimeters of mercury) at some time prior to or during the study.

SUMMARY

1. Pulse volume and skin temperature determinations were made before and after ulnar nerve block from the fifth finger tip of 23 battle casualties admitted to a Mobile Army Surgical Hospital in Korea.

2. Patients who were studied in the higher ranges of environmental temperature revealed smaller increases in pulse volume after ulnar nerve block.

3. Patients studied in the higher ranges of environmental temperature revealed larger initial absolute values for pulse volume.

4. A correlation could not be established between the initial absolute pulse volume value and the administration of morphine prior to the study.

5. Most of the patients studied, when evaluated clinically, were considered to be in a state of slight blood volume deficit. The patients who were more oligemic were too few to compare with this larger group. Consequently, a correlation could not be established between either the initial absolute pulse volume value or the degree of increase in pulse volume after nerve block and the degree of blood volume deficit. However, the patients whose systolic blood pressures were 140 or more millimeters of mercury, all of whom had slight or no blood loss, showed relatively small increases in pulse volume after nerve block.

6. A correlation could not be established between either the initial absolute pulse volume value or the degree of increase after ulnar nerve block and the type of injury, i.e. abdominal or extremity.

7. A correlation could not be established between either the initial absolute pulse volume or the increase in pulse volume after ulnar nerve block and the systolic blood pressure. Six types of blood pressure response were observed in these patients and these are recorded.

8. The case reports and studies on 2 patients with posttraumatic hypertension are presented in detail.

9. Fourteen patients had skin temperature responses which were satisfactory for evaluation. All but 3 of these patients had skin temperatures before ulnar nerve block which were greater than the environmental temperature.

10. There was a tendency for those patients with the highest systolic blood pressures to have lower values for initial absolute temperature before ulnar nerve block.

11. There was a tendency for smaller increases in skin temperature after ulnar nerve block to occur in those patients studied at higher environmental temperatures.

12. The large degree by which these patients failed to reach the theoretical maximal vasodilatation level after ulnar block, for both skin temperature and pulse volume, suggests that oligemia and decreased cardiac output were largely responsible for this deficit. How-

ever, in the 9 hypertensive patients, all of whom had slight or no blood loss, the possibility of a hormonal vasoconstrictor substance being responsible for the major portion of the deficit is discussed. It was not possible to separate the components of the deficit into that attributable to oligemia and decreased cardiac output and that due to humoral vasoconstriction.

13. From this study it can be definitely concluded that the sympathetic nervous system is functionally active in battle casualties. The traumatic and circulatory insults experienced by these patients did not obliterate the functional activity of the sympathetic nervous system. It was not possible to determine the degree of functional activity of the sympathetics which was operative, i.e., normal activity, hypoactivity, or hyperactivity.

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THE MARGINAL ANASTOMOSES OF THE ARTERIES TO THE LARGE INTESTINE

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RECENTLY, surgeons have become more and more interested in the marginal anastomoses of the arteries to the large intestine. A preliminary study several years ago convinced the author that the current teaching about these anastomoses was either inadequate or inaccurate in many ways. Therefore, a series of dissections of the arteries and their communications was begun and this report presents a summary of the results.

MATERIALS AND METHODS

The cadavers were routinely injected with red latex rubber via the left femoral artery. This technique gives an excellent injection of most of the arteries of the body and is much superior to older techniques because the dissection of smaller arteries is greatly facilitated. Only those subjects having a good general injection of the arteries were chosen for special dissection and recording. Of these there were 71 subjects, but, for various extraneous reasons, several areas of the blood supply were recordable in fewer (not less than 62) subjects. The cadavers were all males over 40 years of age with a wide variety of causes of death.

Following the routine opening of the peritoneal cavity, the arteries to the large intestine were carefully dissected either by the author or under his immediate supervision. On large, specially prepared forms, detailed maps were drawn of the arrangement of the superior and inferior mesenteric arteries, their terminations, their every branch to the large intestine, and every anastomotic communication between these branches.

A note was made of the size of each anastomosis at its narrowest site. The anastomoses were graded 0 (completely absent), + (poor), ++(fair), +++(fairly good), ++-++(good), and +++++ (excellent). The categories +(poor) and ++(fair) include all the small communications not larger than terminal arteries on the bowel wall. The +++(fairly good) arterial communications are those that are appreciably larger than the terminal branches to the bowel that spring from them; the ++++(good) are large, extremely competent arteries; and the +++-++(excellent) are arteries approaching the size of the inferior mesenteric artery itself.

Although the parent arteries (i.e., ileocolic, right colic, middle colic, superior and inferior left colic, and superior rectal arteries) were carefully mapped, their arrangement is not a subject of this report. The arrangement of these arteries and that of the final twigs on the wall of the gut have been dealt with by several authors in the past and our findings are substantially in accord with theirs. The paper by Steward and Rankin in 1933 still ranks as the best general survey of the blood supply to the large intestine and gives an extensive list of references. Studies made by Ross (4, 5, 6) in the past few years have complemented those studies made by Steward and Rankin.

For analysis and reporting, 10 consecutive segments or areas along the margin of the bowel—more or less of special surgical interest—were delineated (Fig. 1). These are:

Area 1—between the terminal branch of the superior mesenteric artery and the ileal branch of the ileocolic artery.

Area 2—between the ascending colic branch of the ileocolic artery and the descending branch of the right colic artery.

Area 3—between arborizations of individual branches of the right colic artery halfway up the ascending colon.

Area 4—between the ascending branch of the right colic artery and the middle colic artery; at the hepatic (right colic) flexure.

Area 5—between arborizations of individual branches of the middle colic artery.

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Area 6—between middle colic branches of the superior mesenteric artery and superior left colic branches of the inferior mesenteric artery; at the splenic (left colic) flexure.

Area 7—between arborizations of the superior left colic artery about halfway down the descending colon.

Area 8—between arborizing arteries to the beginning of the pelvic (sigmoid) colon.

Area 9—between branches to the middle portion of the pelvic (sigmoid) colon.

Area 10—between the lowest branches to the pelvic (sigmoid) colon and the superior rectal artery or its branches.

FINDINGS

Most of the marginal anastomotic loops were within an inch of the bowel that they supplied. Although occasionally there were large calibered arteries making short anastomotic loops closer to the stems of the main arteries, these are excluded from the present consideration. The very small anastomoses on the wall of the gut that have been described by Ross (5) are also excluded.

Where the marginal anastomotic channel consisted of a longitudinal series of anastomoses between many branches, the estimation of size was based on the least of the series. Where there was a multiplicity of more or less parallel arcades, the estimation was based on a summation of the sizes of the parallel channels. Such multiple arcades were much more frequent in the pelvic mesocolon than elsewhere, their occurrence being almost the rule in this region. Multiple arcades were found in all of the areas occasionally, but, contrary to the usual teaching, their occurrence in the hepatic flexure was not more frequent than in the remaining areas, not excluding the splenic flexure.

A survey of the maps revealed that there were a great many variations of total pattern. Indeed, the individual patterns showed many differences in details. Often there was a striking variation from one area to the next in the same subject.

The statistical findings are summarized and portrayed graphically in Figure 1. (The percentages are based on the following totals: areas 2, 3, 4, and 5—71 subjects; areas 1 and 6—70 subjects; area 7—69 subjects; area 8—68 subjects; area 9—64 subjects; area 10—62 subjects.)

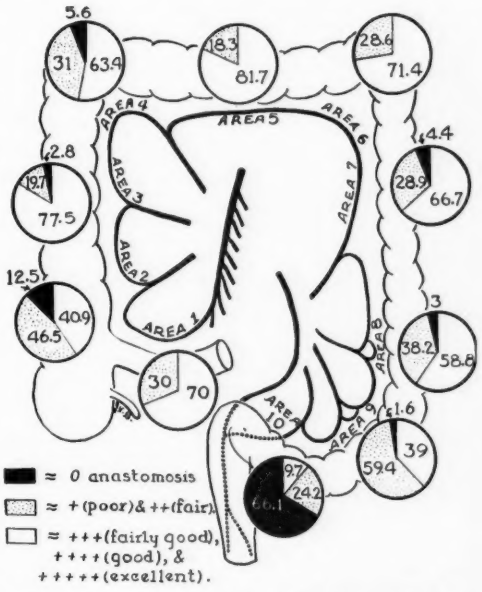

Fig. 1. Ten consecutive areas along the margin of the gut with a graphic representation of the percentage incidence of three classes of anastomoses in each area.

DISCUSSION

The findings in this series are in agreement with current descriptions of the marginal anastomoses only in a general way.

There is a strikingly high proportion—two-thirds—of total absence of anastomosis between the superior rectal artery and the last branches to the pelvic (sigmoid) colon. Sunderland emphasized this fact in 1942, finding that in only 5 of his 25 cases was any anastomosis present. Drummond, who first focussed attention on the marginal arteries in 1914, found either a poor anastomosis or no anastomosis in the terminal sigmoid region in half of his 20 subjects.

The cecal area (area 2) is the only other one with a high frequency of absence of anastomosis. Here, more than 1 out of every 10 subjects have no anastomotic communication. However, this area receives such a profusion of terminal branches from the ileocolic artery that the occasional lack of anastomosis is

hardly of practical importance. Most of the areas show a small incidence of total lack of anastomosis, and it is probably safe to predict that such a lack is not impossible in any area.

Areas 1, 3, 5, 6, and 7 show the greatest numbers of good anastomoses, but it must be emphasized that in each area there is an appreciable number of poor or only fair anastomoses. The findings for area 5 (splenic flexure)—where the anastomosis is generally good—are especially significant because of their marked variance with past teaching. During the past year Goligher (3) reported a clinical series essentially in accord with this. This same author reported (2) the arrangement of the branches of the inferior mesenteric artery at an earlier date but made no note of the anastomoses.

Steward and Rankin found a union between the middle colic artery and upper left colic artery in all of their cases but no details are available. They reported that the marginal anastomotic channel from ascending colon to sigmoid colon was continuous in 95 per cent of 40 specimens, although it was slight in certain areas of several specimens. Ross (4) seems to concur with these findings in a general way.

Although the present method of demonstrating the size of the arteries is superior to earlier techniques, no attempt is made here to suggest that the anatomic arrangement necessarily indicates the physiologic state of the anastomoses. Moreover, additional factors, such as spasm and "kinking" of the arteries, may reduce the effective circulation following various surgical procedures involving the gut.

SUMMARY AND CONCLUSIONS

1. A series of 71 dissections of the arteries to the large intestine was made in adult male cadavers. The arteries of the entire body had been injected with red latex rubber.

2. This paper presents a summary of the findings in regard to the size of the marginal anastomoses in each of 10 consecutive segments or areas from terminal ileum to the rectum.

3. Except for the area between the last branches to the pelvic (sigmoid) colon and the superior rectal artery, the anastomoses were generally good.

4. On the other hand, this series shows that one must not take for granted that the anastomosis in any area is always good. Indeed, it may be absent or very poor in areas where it is usually thought of as adequate.

5. Examination of one part of the marginal anastomoses gives little if any indication of the character of the anastomoses in other, even neighboring, areas.

6. Although, statistically, the surgeon can expect a good anastomosis everywhere except in the rectosigmoid area, he should treat every case individually, examining the anastomoses carefully along the whole length of bowel with which he is concerned. He must remember also that factors other than the anatomic size of the anastomoses may play an important role in determining the effective circulation.

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ENDOCRINE INTERRELATIONS CONCERNED WITH THE POSTOPERATIVE RENAL RESPONSE TO A WATER LOAD

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PART A.—THE EFFECT OF THYROXINE ON THE RENAL RESPONSE TO A WATER LOAD IN HUMANS FOLLOWING STRESS

A COMPARISON of the alterations in the physiologic readjustments subsequent to stress with those following the administration of pituitary adrenocorticotrophic hormone (ACTH) or adrenocortical extract (ACE) has been made by many observers, principally Moore. The concept of a responding pituitary adrenocortical axis as the primary cause of the homeostatic alterations subsequent to stress has become entrenched in clinical thinking; however, recent reports point to a mechanism involving a complex of thyroid and adrenocortical interrelationships. It appears from the studies of Goldenberg and White and their associates that there may be an increase in thyroid activity following trauma; on the other hand, demonstrations have been made by Williams and his co-workers of a decrease in thyroid activity during stress, and by Zwemer of an antagonism between adrenocortical and thyroid function. Goldenberg and associates have presented evidence that a thyroid stimulation-inhibition sequence exists in which the initial thyroid stimulation response is replaced by depression of this gland's activity coincident with any increase in adrenocortical activity. Depression of thyroid function probably occurs either by action directly on the thyroid gland or by depression of pituitary release of thyroid stimulating hormone (TSH). Further evidence of the complexity of the total neuroendocrine response to trauma is the demonstration by Engle (1, 2) that adrenalectomized animals maintained on a fixed amount of exogenous adrenocortical extract were able to react with increasing increments of metabolic response to increasingly stressful stimuli. These same animals, however, when denied exogenous ACE were unable to react to stress, implicating the adrenocortex as necessary in the initiation but not necessarily in the magnitude of the response. Absence of the thyroid gland, additionally, prevents the usual stress deviations as shown in rats that nitrogen loss following burns is abolished if preceded by thyroidectomy. The catabolism of tissue protein, moreover, during the stress of fasting is greatly diminished by prior thyroidectomy. All this evidence strongly suggests an interrelationship between the thyroid, the adrenocortical, and the pituitary glands. The thyroid response and, therefore, the point in time at which antagonism occurs, varies widely between individuals. The fact that debilitated patients respond differently to trauma with little or no rise in corticosteroid output could be explained by the absence of an initial thyroid response.

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PART B.—THE EFFECT OF A CARBONIC ANHYDRASE INHIBITOR ON THE RENAL RESPONSE TO A WATER LOAD IN HUMANS FOLLOWING STRESS

Major metabolic alterations following stress are concerned with variations in water and electrolyte excretion. Yet the fundamental nature of these changes is poorly understood. Several factors are probably responsible. Antidiuretic hormone (ADH) may be released by the posterior pituitary gland in emotional stress or by an increase in the osmotic pressure of arterial blood despite the reported demonstration of less than expected amounts of ADH in the urine of subjects during the postoperative period. A complete inhibition of ADH release from the posterior pituitary gland can be achieved by obtaining a positive balance

of water in normal subjects. During a response to trauma, however, a positive balance still may be associated with further retention of water indicating that another factor is responsible; this factor is considered to be adrenocortical in origin. The site of corticosteroid activity is thought to be on the renal tubule but is as yet unproved. It was thought possible that a study involving the use of a carbonic anhydrase inhibitor (6063, diamox) during stress or after the administration of ACTH would help to demonstrate the site of action of the corticosteroid. The action of carbonic anhydrase is well known and consists essentially of an exchange of sodium for hydrogen ions in the renal tubule thus helping to conserve fixed base. Inhibition of this function by diamox occurs in normal subjects, but investigations during stress have not been reported. It was reasoned that if carbonic anhydrase inhibitor could cause natruresis during the stress response, then the action of corticosteroids presumably occurred at the tubular level by facilitating the enzyme action and was inhibited by the drug.

METHODS

The following studies were made on both control and postoperative subjects: serum and urine sodium and potassium concentrations, *p*H, osmolarity, titratable acidity, creatinine, urinary corticosteroids, and urine volume. Each of these determinations, except corticosteroids, was made at hourly intervals during the 4 hour period of a constant intravenous infusion of 5 per cent glucose in distilled water at the rate of 250 cubic centimeters per hour. All studies were carried out in a constant temperature and constant humidity room to avoid variations in insensible loss. Subjects were fasting and basal during the testing period. The following schedule was employed for control and experimental studies:

Control. Part A.—Two volunteer medical students in good health, of average height and body mass, were studied. A diet of 3,000 calories daily was employed and the 24 hour oral fluid intake was constant.

Day 1. Water load alone with hourly blood and urine studies was done; 1,000 cubic centimeters of 5 per cent glucose in distilled water was infused intravenously at a constant rate of 250 cubic centimeters per hour.

Day 2. ACTH (30 units) in the water load was given. No studies were performed; the ACTH was given only to secure preliminary maximal adrenocortical stimulation.

Day 3. ACTH (30 units) in the water load were given and blood and urine studies performed.

Day 7. Three days were allowed to elapse after ACTH administration to insure absence of excessive adrenocortical stimulation. On day 7 the subjects received the water load containing 4 milligrams of l-thyroxine intravenously. Blood and urine studies were performed.

Day 8. ACTH in the water load was repeated without measurements being made; this again served as a period for maximal adrenocortical stimulation.

Day 9. The water load containing 30 units of ACTH and 4 milligrams of l-thyroxine was administered and blood and urine studies were performed.

Part B.—Three controls were employed, and again these were medical students of average size and in good health, maintained as in Part A.

Day 1. Water load alone was given at the usual rate of 250 cubic centimeters per hour for 4 hours, and blood and urine studies were performed.

Day 2. Water load and 4 grams of diamox were administered orally. The diamox was given as 1 dose immediately preceding the start of the intravenous infusion; blood and urine studies were performed.

Day 3. The water load containing 30 units of ACTH was given. No studies were performed.

Day 4. The water load containing the ACTH and preceded by a dose of 4 grams of diamox orally were administered and blood and urine studies performed.

Experimental. Part A.—This part consisted of exactly the same procedures as were performed on the controls; however, operative procedure was substituted for ACTH administration. The patients used were: Case 1, F.R., a 61 year old white male, who had a large adenocarcinoma of the stomach and underwent gastrectomy; Case 2, A.S., a 60 year old colored female with a large sigmoid neoplasm, who had a partial colectomy and colostomy performed; Case 3, A.D., a 35 year old white male, who underwent a subtotal gastrectomy for a bleeding duodenal ulcer.

Day 1 (preoperative day). The water load was given and hourly blood and urine studies were done.

Day 2 (first postoperative day). The test water load was given and hourly studies were performed.

Day 3 (second postoperative day). The test water load containing 4 milligrams thyroxine was given and hourly studies performed.

Part B.—One patient was studied. Operation was substituted for ACTH administration. Case 4, E.B., a 25 year old white female with sarcoma of the right gluteal region and extension to the inguinal region, who underwent a right radical groin dissection.

Day 1 (preoperative day). The test water load was given and hourly studies were performed.

Day 2 (first postoperative day). Water load and hourly studies were performed as in the preoperative study.

Day 3 (second postoperative day). The test water load was given intravenously preceded by 4 grams of diamox given orally; blood and urine studies were performed.

RESULTS

Graphs representative of composite results have been used to demonstrate the percentage changes from control periods occurring during the variable conditions. Measurements not considered to have shown significant changes and, therefore, not presented are: serum *p*H, serum and urine potassium, serum and urine creatinine. Endogenous creatinine clearances were determined, and revealed normal renal function in all cases.

Control study. A study in which ACTH is substituted for operative trauma. Part A.—The effects of thyroxine. Figure 1 demonstrates the urinary corticosteroid excretion under the various programs. These are recorded as percentage changes from the control period of the simple water load. ACTH administration increased the urinary excretion of corticosteroid but an even greater increase was occasioned by the administration of thyroxine intravenously. The administration of thyroxine and ACTH together produced the largest increase in urinary excretion of corticosteroids.

A study of the urinary volume during the 4 hour period of study showed that there was a remarkable reduction in urinary volume as a result of the intravenous administration of ACTH in the water load. This is reflected in the 24 hour urine volume which is reduced during the day of ACTH administration. It

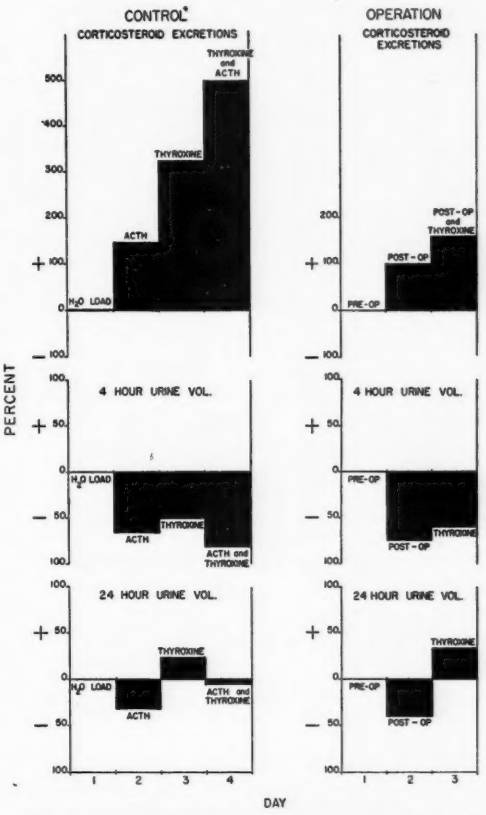

Fig. 1. Representative composite changes in urine volume flow and corticosteroid levels for the control and experimental subjects given thyroxine.

is important to note that, while thyroxine reduced the water retention during the period of the 4 hour study, in the 24 hour recordings of water balance thyroxine actually induced a diuresis. When ACTH and thyroxine were simultaneously administered the 24 hour urine volume was within experimental limits, the same as the control day of observation. Thus it is apparent that, though thyroxine and ACTH simultaneously administered produced the highest level of corticosteroidal excretion observed, the 24 hour urine volume for the day was the same as the control period.

Serum sodium levels in this same control study were noted as shown in Figure 2. The administration of a simple water load caused

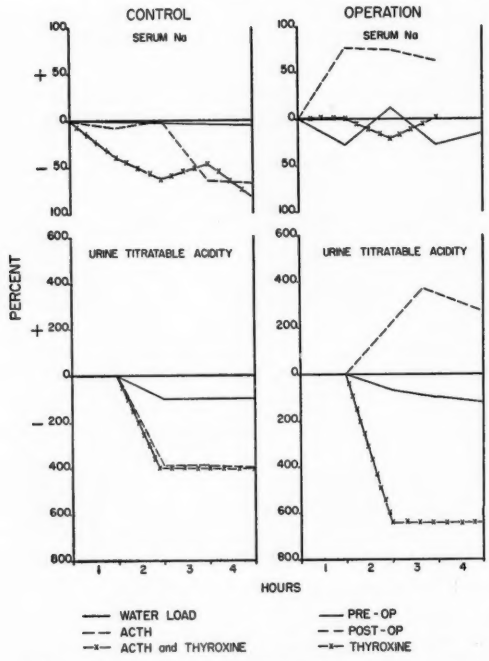

Fig. 2. Representative composite changes in the serum sodium and urine titratable acidity for the control and experimental subjects given thyroxine.

no essential change in the serum levels of sodium. The intravenous administration of ACTH simultaneously with the water load showed no essential change for the first 2 hours of study, during which time 500 cubic centimeters of water had been administered intravenously. As the infusion continued there was a prompt fall in the serum sodium level. On the other hand, the administration of thyroxine simultaneously with the ACTH showed a progressive fall from the very initiation of the intravenous infusion of water.

Observations made on the urine osmolarity, as demonstrated in Figure 3, show that under the influence of a constant infusion of water there is a very marked and progressive fall in the urine osmolarity as might well be anticipated. When, however, ACTH was administered simultaneously in the water load there was less of a fall in the urine osmolarity which would mean that the ionic concentration of the urine was remaining essentially the same even though, as previously recorded, the volume was significantly decreased. During the last hour of the observations when ACTH was given there was a prompt fall in the urine osmolarity, indicating a selective but delayed excretion of water over electrolyte. When ACTH and thyroxine were administered simultaneously complete reversal of the situation as far as urine osmolarity is concerned was obtained. The urine osmolarity progressively rose during the observations when these two hormones were supplied simultaneously, indicating that there was a selective increase in ionic excretion over water.

The observations recorded in the previous paragraph are well borne out in the measurement of urine sodium under these various conditions as recorded in Figure 3. It is noted that under a water load there is a progressive increase in urine sodium which, correlated with the very little, if any, change in serum sodium, means that sodium must be mobilized from some extravascular source for this to occur. The administration of ACTH with the water load caused first a slight increase in the urine sodium over the first hour of observation and then a prompt fall, as might be expected, the adrenocortical steroid activity causing sodium retention. It is very interesting to observe that when thyroxine and ACTH are simultaneously administered the sodium retention as reflected in urinary excretory measurements is quite reversed and that the amount of sodium in the urine increases tremendously toward the latter part of the fourth hour period of observation.

Observations under similar circumstances of urine titratable acidity, as shown in Figure 2, show that with the administration of a water load there is a small and constant reduction through the observation period. When, however, ACTH is simultaneously administered with the water load, there is an accentuated fall in the urine titratable acidity which remains fairly constant throughout the last 2 hours of observation. When ACTH and thyroxine are simultaneously administered there is no great change from when ACTH is administered alone with the water load.

Part B.—The effects of diamox. When the water load is given to the controls in this

portion of the study the results are essentially as those already described for the control group under the ACTH section.

In Figure 4 are diagrammed the representative percentage changes in corticosteroid excretion, 4 hour urine volume, and 24 hour urine volume under the various phases of this control study. It is most interesting to find that the administration of diamox caused a reduction in urinary corticosteroid excretion. As was to be expected, ACTH significantly increased the 4 hour corticosteroid excretion; when the water infusion was given containing ACTH but preceded by oral diamox, there was again significant reduction in the urinary corticosteroid excretion.

Both the 4 hour urine volume and the 24 hour urine volume were tremendously increased at the time that diamox was given orally. During the administration of ACTH in the water load, both the 4 hour and the 24 hour urine volumes were significantly below that of the control period. When, however, oral diamox preceded the ACTH infusion of the water load the 4 hour urine volume was not greatly dissimilar from that of the ACTH period. On the other hand the 24 hour urine volume was tremendously increased as though there was a reversal of the ACTH water retention by the administration of diamox.

Serum sodium changes under the various aspects of this control investigation are portrayed in Figure 5. It is noted that the serum sodium changes very little under the simple administration of the water load. However, when the water infusion is preceded by the oral administration of diamox, for approximately the first 2 hours of the infusion there is a tremendous rise in serum sodium. In the latter half of the study period there is a significant fall in serum sodium levels below those found at the beginning of the study. The pattern of serum sodium levels when ACTH is given in the infusion is essentially the same as was described for the other control series of experiments. When, however, the infusion or water load containing ACTH is preceded by the oral administration of diamox, an effect very similar to that seen when ACTH and thyroxine are given together (Fig. 2) is observed; the reversal is demonstrated by an

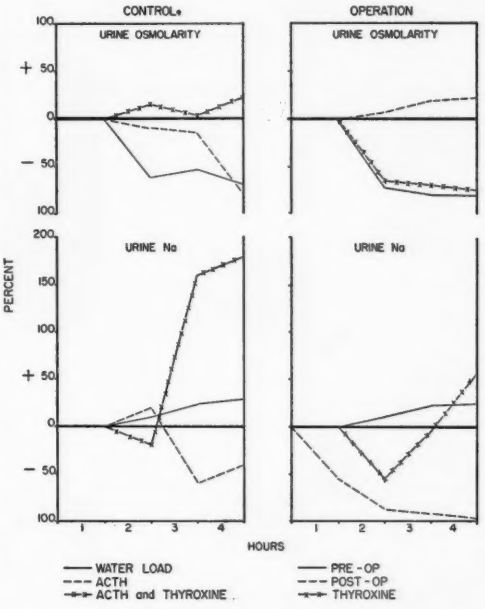

Fig. 3. Composite correlative changes between urine osmolarity and urine sodium for control and experimental subjects given thyroxine.

initial prompt progressive fall in serum sodium level.

When the serum sodium changes are compared with the urine osmolarity changes as shown in Figure 6, some correlations can be made. The urine osmolarity under the effect of the simple water load is as has been described previously. When the water infusion is repeated and preceded by the oral administration of diamox no essential difference is noted. Thus the ionic concentration of the urine in response to a water load is not affected by the oral administration of diamox. If, however, the intravenous infusion contains ACTH, it is noted that the urine osmolarity changes very little, much less of a decrease than occurred under a simple water load, indicating nearly iso-osmotic retention of water and electrolytes, irrespective of the urine volume. It is only toward the end of the period of observation that the urine osmolarity under ACTH administration falls sharply to levels of significance. When, however, the water load contains ACTH but is preceded by the

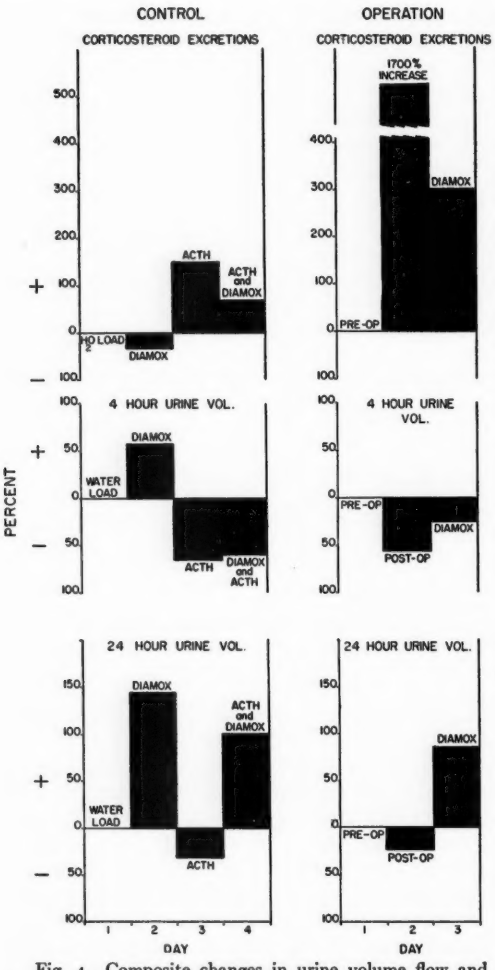

Fig. 4. Composite changes in urine volume flow and corticosteroid levels in control and experimental subjects given carbonic anhydrase inhibitor.

oral administration of diamox urine osmolarity values fall intermediate between the two areas shown in this figure. This would suggest an antagonistic renal tubular effect between ACTH and diamox.

Urine sodium determinations, as illustrated in Figure 6, show the usual findings with a water load without experimental manipulation. When the water load is preceded by oral diamox it is seen that the urine sodium increases very significantly above the levels obtained with the ordinary water load. Since in the previous discussion it was pointed out that urine osmolarity was not much different whether diamox was present or not, it can only be assumed that the ionic concentration stayed the same and some other ion was substituted by sodium in the excretory mechanism. The administration of ACTH produces a pattern that has previously been described in the normal individuals. However, when ACTH and diamox are administered in that the ACTH is contained in the infusion medium and is preceded by a dose of oral diamox, it is seen that almost the normal urinary sodium response to an infusion load is present, in that there is no early change in the urinary sodium level and only a late rise as is characteristic of a water load alone. This again emphasizes the possibility of an antagonistic effect between ACTH and diamox on the renal excretion of electrolytes.

An examination of the results in urine titratable acidity determination under these circumstances presents interesting findings as shown in Figure 5. The usual response of a small fall and a plateau in the urine titratable acidity as a response to an infused water load is shown. If diamox precedes the water infusion no great change is noted in the urine titratable acidity. However, as has been described before, when ACTH is given in the infusion fluid a significant fall in urine titratable acidity occurs, the plateau is reached early and continues out through the period of the observation. However, when the ACTH is contained in the infused fluid and is preceded by oral administration of diamox, a very prompt, rapid, and progressive fall to a zero value for the titratable acidity is obtained, so that in this respect ACTH and diamox are not antagonistic.

Experimental study. A study in which ACTH is replaced by operative trauma. Part A.—The effects of thyroxine. Corticosteroid excretion was increased significantly in the immediate postoperative period as shown in Figure 1. With the further addition on the second postoperative day of thyroxine to the water load infusion, there was an additional increase in corticosteroid excretion. As might be anticipated, the 4 hour urinary volume was

significantly less in the immediate postoperative period than the control preoperative determination. When thyroxine was administered to the infusion load in the immediate postoperative period it showed less of a decrease in the urinary volume. If the 24 hour urinary volumes are inspected it is noted that there was less water put out in the immediate postoperative period than preoperatively and, on the contrary, when thyroxine was administered in the water load there was a diuresis to a degree exceeding the preoperative study. This diuresis occurred even in the face of a significantly increased corticosteroid excretion over the first day postoperatively.

The serum sodium levels are of equal interest as illustrated in Figure 2. The preoperative determinations under the effect of a water load showed that the serum sodium levels fluctuated roughly about a normal level. When the water load was repeated while the subject was under the influence of a response to a traumatic episode, it is noted that the serum sodium levels increased very significantly. When the test water load was given again but contained thyroxine the serum sodium levels did not change significantly. Thus there was a reversal of serum sodium alteration to normal by the simultaneous administration of thyroxine, even though the subject was under the influence of a metabolic response to trauma.

The preceding findings are of even greater significance when the urine osmolarity studies are interpreted (Fig. 3). The preoperative water load showed a progressive fall to a plateau in the urine osmolarity values under the influence of the continued diuresis. A contrary finding in the immediate postoperative period was a progressive rise in the urine osmolarity in response to the water load. This, too, when repeated with the administration of thyroxine in the infusion medium was found to be reversed toward the preoperative finding.

A reciprocal relationship is found between urine osmolarity and urine sodium in relation to operation (Fig. 3). The preoperative determination showed a progressive rise in the urine sodium concentration which was in contradistinction to that found in the immediate postoperative period when an infusion was

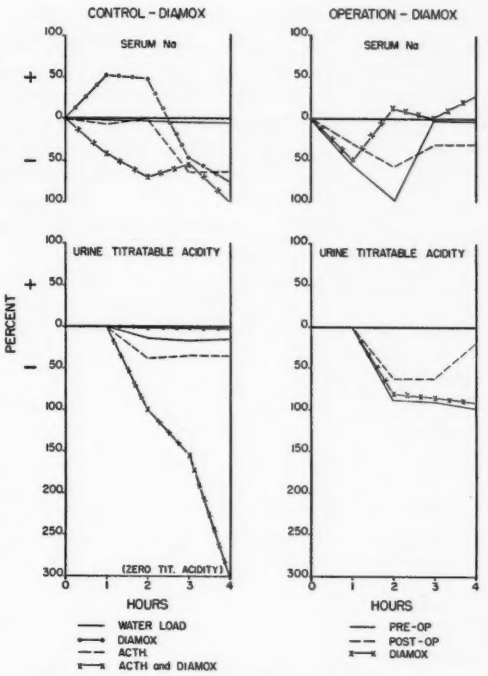

Fig. 5. Composite changes in serum sodium and urine titratable acidity in control and experimental subjects given carbonic anhydrase inhibitor.

followed by a prompt, progressive, and rapid fall in urine sodium concentration under the influence of water diuresis. When the infusion contained thyroxine in the immediate postoperative period a trend toward the reversal of the postoperative finding was found in that the urine sodium concentration tended back toward the plateau of no change.

In Figure 2 the urine titratable acidity as affected by operation is quite significant. The preoperative determination was essentially the same as for all the controls. The postoperative response showed a tremendous increase in urine titratable acidity under the effects of a continued water diuresis. This increase in urine titratable acidity could be completely reversed and thrown in the opposite direction, as a matter of fact, by the simultaneous administration of thyroxine. It is to be emphasized that all the findings that were found 24 and 48 hours postoperatively were done at

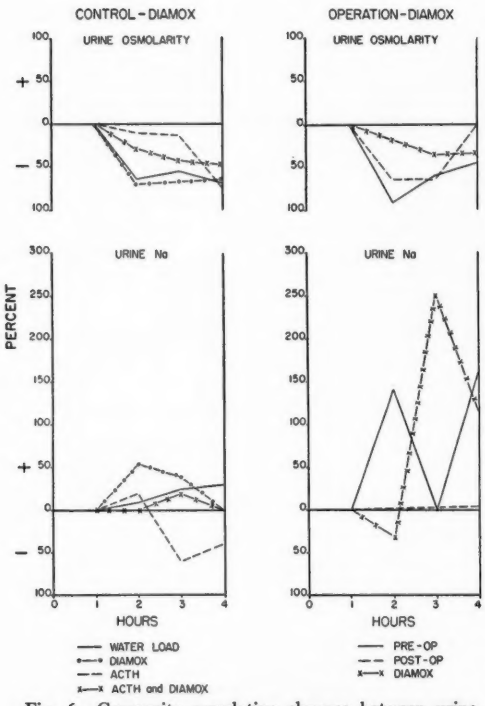

Fig. 6. Composite correlative changes between urine osmolarity and urine sodium in control and experimental subjects given carbonic anhydrase inhibitor.

the time that the corticosteroid excretion was from 100 to 150 per cent greater than the control preoperative level.

Part B.—The effects of diamox. An examination of Figure 4 reveals that the administration of diamox reduces the corticosteroid excretion while the patient is in the adrenocortical phase of response to trauma. Similarly, diamox restores more closely to the preoperative levels the 4 hour urine volumes in response to the constant water infusion. When the 24 hour urine volumes are charted it is noted that there is a complete reversal to the extent of an unusually large diuresis when diamox is administered even though the corticosteroid excretion is still far above the preoperative level. Thus it appears that the diamox can produce diuresis in the face of increased adrenocortical activity.

The effects on serum sodium levels are shown in Figure 5. The preoperative levels of serum sodium under the influence of a continuous water infusion show a small abnormality in response which consists of an initial fall in the serum sodium level but with a prompt return to normal. The postoperative response resembles greatly that seen following ACTH in that there is a fall and a plateau reached by the time of the termination of the infusion. The administration of oral diamox prior to the administration of the water load, even though there is still a significant level of adrenocortical activity shows a distinct reversal by diamox of the serum sodium levels in that the serum sodium levels remain high after an initial fall and actually are the reverse of the ACTH effect. As a matter of fact, the serum sodium levels rise higher with diamox than they do after the administration of a water load preoperatively.

Figure 6 demonstrates the alterations in the urine osmolarity under the various phases of this investigation. Preoperatively there is the anticipated sharp fall in urine osmolarity because of the selective secretion of water and selective facultative reabsorption of the sodium ion. The ACTH effect shows less of a fall in the urine osmolarity during the course of the water infusion. When diamox is given orally preceding the intravenous infusion, it is noticed that there is less of a change in the urine osmolarity.

The urine sodium levels are shown in Figure 6. There is a large amount of sodium excreted in the preoperative period under the influence of a constant infusion of water. In the immediate postoperative period, however, adrenocortical activity is at a high level and there is very little sodium excreted. When the water infusion is preceded by the oral administration of diamox there is a tremendous increase toward the latter part of the study in the urinary excretion of sodium. This finding would seem to indicate that there was some antagonism between the effects of ACTH and diamox as far as the urinary excretion of sodium was concerned.

These findings are all very interesting, particularly when viewed in the light of the values found for the urine titratable acidity under the various influences as shown in Figure 5. The preoperative study shows that

there is a prompt fall in urine titratable acidity which soon reaches a plateau and continues at that level. When the patient is studied in the postoperative period with a high level of adrenocortical activity there is less of a decrease in urine titratable acidity with some recovery as the infusion progresses. The prior administration of diamox, however, significantly returns the level of urine titratable acidity to that seen in the preoperative period even though corticosteroid excretion is significantly increased at this time.

DISCUSSION

The concept that the metabolic alterations subsequent to stress produced by trauma are exactly like the metabolic effects produced by the exogenous administration of adrenocorticotrophic hormone is not entirely true. There are many similarities, however, as pointed out by the results of this study. For example, the administration of adrenocorticotrophic hormone and the experience of the traumatic episode such as an operation produced significant increases in the urinary excretion of adrenocortical hormone urinary metabolites. Similarly, there is a significant decrease in both a short period of measured urinary volume as well as in the 24 hour urinary volume of water occasioned either by ACTH or a traumatic episode. It is interesting to compare the effects on the serum sodium level of the constant infusion. As the infusion progresses, ACTH produces a significant fall in the serum sodium level. On the other hand, when a water infusion is given over a prolonged period of time in the immediate postoperative period, there is a progressive rise in the serum sodium levels under this influence. The measures of urine titratable acidity show that the effect of a constant infusion of water containing ACTH shows a very significant fall in the measurable urine titratable acidity. On the other hand, when the infusion is given in the immediate postoperative period there is a rise in the urine titratable acidity.

Insofar as considering measurements of urine osmolarity which measure total osmotically active particles it is interesting to note the administration of ACTH causes a delayed fall in urine osmolarity under the influence of continued infusion of water. This can only mean that there is a selective retention of osmotically active particles or a selective excretion of water in order that the osmolarity will fall. It is true, however, that the osmolarity does not fall as promptly as it does with the simple water infusion without the addition of ACTH. Contrasted with the postoperative measurements of urine osmolarity, there is a gradual but distinct rise in urine osmolarity, meaning the selective secretion of electrolytes or concentration of the urine in that period. That this is not entirely due to the sodium ion is shown well by comparing the measurements of the urinary excretion of sodium under the two contrasting situations. Both operation and the administration of the adrenocorticotrophic hormone affect the urine sodium in that it progressively falls during the course of a diuresis. Therefore, the osmolarity changes must be associated with other molecules having an osmotic effect other than the sodium ion. Since it was found that potassium level excretion in the urine did not change significantly in the course of the study, it must be associated with some other ion or osmotically active particle.

In an effort to evaluate thyroid adrenocortical relationships in this study, thyroxine was given intravenously as has been indicated. It has been shown adequately that as far as urinary volume both in the short period of observation and the 24 hour total for the day of the study that the simultaneous administration of thyroxine will reverse both the ACTH and operative water retention effect.

There are many points of difference, however, between operation and ACTH as far as thyroxine reversal is concerned. Thyroxine does not reverse the changes in the serum sodium levels due to water diuresis. The simultaneous administration of thyroxine does not alter the changes in urine titratable acidity that results from the administration of ACTH. Similarly, thyroxine does not reverse the urine osmolarity findings. It is of interest that simultaneous administration of ACTH and thyroxine does reverse the ACTH induced fall in urinary sodium excretion levels.

When thyroxine is used at the time that operation is substituted for the administra-

tion of ACTH, it is interesting to note that thyroxine does reverse the operative effect on the elevation of serum sodium levels under water infusion. Similarly, thyroxine reverses the urine titratable acidity changes that occur in the postoperative period as well as the measured changes in urine osmolarity. The measurement of urinary excretion of sodium is, as in the ACTH study, reversed by the administration of thyroxine in the postoperative period.

It is considered that diamox is a specific carbonic anhydrase inhibitor. Therefore, any reversals that might occur in renal tubular function by administration of diamox would be considered to be processes influenced by the action of the specific carbonic anhydrase enzyme in the renal tubular epithelium. For some unknown reason it appeared that diamox reduced the urinary metabolites of adrenocortical hormone either when the adrenocortex was stimulated by exogenous ACTH or by operative trauma. Specifically, diamox was able to reverse the water retention effects of both ACTH and operation, reducing the water retention in the short period of observation and producing a diuresis above the control levels in the 24 hour urine volume measurement.

When ACTH was given, diamox actually accentuated the changes in urinary titratable acidity that was occasioned by the administration of the hormone. However, in the postoperative period the administration of diamox did reverse the effects that resulted from the physiologic responses to the operative trauma. Diamox did tend to reverse the changes in urine osmolarity that resulted from the administration of ACTH but did not change those that resulted from operative trauma in the same sort of study. However, urinary excretion of sodium was reversed toward normal in the ACTH study and also in the one measuring the response to operative trauma.

Since both the simultaneous administration of thyroxine with ACTH or under the influence of operative trauma, as well as diamox, appeared to counteract some of the effects of hormone administration or stress, it would appear possible to suggest that the adrenocortical hormone and thyroxine had their effect on either facilitating or inhibiting the action of carbonic anhydrase. It would appear that adrenocortical hormone facilitates the activity or accentuates the effect of the carbonic anhydrase while thyroxine and diamox both are antagonistic to its activity.

CONCLUSION

1. It is not safe to predict that all of the metabolic alterations, particularly those relating to renal activity, occurring in the immediate posttraumatic period reflect solely the action of the pituitary release of ACTH and the subsequent stimulation of the adrenocortex. Many of these metabolic deviations from normal are not specifically related to the activity of adrenocortical hormone alone.

2. It is suggested that many of the metabolic effects are specifically related to an interrelationship that exists between the thyroid and the adrenocortical activity.

4. It is suggested that the renal effect of adrenocortical and thyroid hormones is related to their action on the enzyme carbonic anhydrase in the renal tubular epithelium.

5. Many of the observations made are not explicable on the basis of any known mechanism at the present time.

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DIVERTICULITIS AND CARCINOMA OF THE COLON

Differential Diagnosis

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IN OVER 60 per cent of all patients with carcinoma of the rectum and colon the lesion can be palpated on rectal examination or be seen on sigmoidoscopic examination. In the majority of the remaining 40 per cent of patients with carcinoma of the large bowel, the lesion involves the lower sigmoid or lower descending colon. In a review of 1,457 patients with malignant lesions of the colon and rectum as seen at the clinic (1), almost half of the carcinomas above the rectal segment occurred in the rectosigmoid and sigmoid areas. Morton stated that 25 per cent of all carcinomas of the colon occur in the sigmoid area. It is in this same area that practically all diverticulitis of the colon develops.

Patients with carcinoma of the colon and with diverticulitis fall into the same age group. The three cardinal symptoms of carcinoma of the sigmoid, namely, left lower quadrant pain, change in bowel habit, and rectal bleeding, are the typical symptoms of patients with diverticulitis of the colon. In patients with carcinoma or diverticulitis, obstructive symptoms, such as colicky pain, distention, anorexia, and even vomiting are likely to develop. Tenderness may develop and a palpable mass may be found in the left lower quadrant in patients with either carcinoma or diverticulitis. On proctoscopic examination of patients with diverticulitis, suggestive signs of diverticulitis may be noted but they rarely permit the definite establishment of the diagnosis. The proctoscopic examination may be negative in patients with carcinoma as low as the rectosigmoid area owing to fixation and angulation of that segment of the colon by the malignant growth.

If the barium enema film reveals a long, narrowed area in the sigmoid with marked spasm, as indicated by the "picket fence" appearance produced by the barium, it is very suggestive of diverticulitis. Occasionally the roentgenologist may discern the preservation of the mucosal pattern throughout the involved area, which is also indicative of diverticulitis rather than carcinoma. It must be remembered that diverticulosis, as indicated by the filling of diverticula with barium, is a relatively common condition, and does not in any way rule out the presence of cancer. Welch and associates have pointed out that diverticulosis occurs in 7 to 8 per cent of the general population, and in the age group in which carcinoma is found, two-thirds of all patients having a barium enema will show diverticulosis. If there is a sharp, clear-cut area of narrowing with a loss of mucosal pattern and typical lipping of the defect, a presumptive diagnosis of carcinoma of the colon can be made. Frequently, however, even after careful barium enema study, the roentgenologist is unable to distinguish with certainty between diverticulosis and carcinoma. Schatzki, in an excellent review of this aspect of the problem, concluded that the roentgenologic differential diagnosis between the two diseases was easy in most cases, difficult in some, and impossible in a few.

Rowe and Kollmar, in a collective review of 62 patients in whom diverticulitis and carcinoma occurred simultaneously, have summarized the usual roentgenologic differences between the two diseases, as shown in Table I. It should be emphasized, however, that none of these differences is pathognomonic of carcinoma or diverticulitis. One or more of the roentgenologic characteristics listed under diverticulitis may be found in a patient with carcinoma and vice versa. It should also be pointed out that if more than one examination is necessary to distinguish between diverticulitis and carcinoma, the examination should be repeated within a few weeks and if carcinoma can still not be excluded, surgical intervention should not be further delayed.

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TABLE I. — ROENTGENOGRAPHIC FINDINGS*

Diverticulitis	Carcinoma
1. Spastic bowel with wide transversely arranged folds. "Saw-tooth defect"	1. Bowel adjacent to tumor mass is usually normal
2. Cone-shaped ends to constricted areas	2. Sharply defined margins of lesion, often with overhanging edges. "Shelf-like defect"
3. Long segments of involved bowel	3. Short segments of involved bowel
4. Preservation of the mucosal folds	4. Destruction of mucosal folds
5. Change in size of the constricted area between examinations	5. Tendency toward increasing obstruction between examinations
6. The presence of diverticula	6. The absence of diverticula
7. Flexibility at cone-shaped ends as seen by a changing lumen during a single examination	7. Typical deformity is frequently a convex filling defect
8. Obstruction without demonstrable tumor	8. Obstruction with evidence of tumor mass

*From Rowe, R. J., and Kollmar, G. H. (7)

Pemberton, Black, and Maino found that carcinoma could not be excluded by clinical means in 25 per cent of their 389 cases. Morton stated that, when the diagnosis is in doubt, it is fair to give a reasonable medical trial in the hope that the inflammation may subside. We agree with his conclusion that in case a differential diagnosis cannot be made clinically between diverticulitis with complications and cancer of the sigmoid with complications, an exploratory operation is indicated. Morton further pointed out that as diverticulitis and carcinoma of the colon become more advanced and complicated by perforation and surrounding inflammatory reaction, the differential diagnosis becomes increasingly difficult.

Even with the abdomen open at the time of laparotomy and after careful inspection and palpation of the lesion, the surgeon is frequently unable to distinguish between diverticulitis and carcinoma of the sigmoid colon associated with a marked secondary inflammatory reaction. If the preoperative diagnosis was equivocal, this places the surgeon in a situation he would prefer to avoid if possible. When he has preoperative evidence that the process is diverticulitis and the inflammatory reaction is acute, such as is associated with perforation and abscess formation, or when a fistula into the bladder is present, he may prefer to do a transverse colostomy and allow the acute process to subside. If he elects to do only a transverse colostomy but cannot exclude carinoma either before or after the initial procedure, he must proceed with resection within 2 to 3 weeks, long before the inflammatory reaction associated with severe diverticulitis will have subsided. Resection of the sigmoid under these circumstances is often a difficult procedure and associated with a definitely higher morbidity and mortality rate. On the other hand, if carcinoma can be excluded and resection of the involved sigmoid and lower descending colon is carried out after an interval of 6 to 9 months when the inflammatory reaction has completely subsided, it becomes a relatively simple procedure and, as shown by Colcock (3) and Sedgwick, can be done with a minimal risk to the patient.

Boyden, Welch, Colcock (4) and others have pointed out in recent years that earlier surgical intervention in persistent or recurrent diverticulitis will permit the more frequent use of a one stage resection and at the same time reduce the over-all morbidity and mortality associated with diverticulitis of the colon. If the operative conditions are such that a primary resection and anastomosis are feasible, and one can be fairly certain that the lesion is not malignant, a segmental resection, removing all of the involved colon but preserving the inferior mesenteric artery, may be carried out.

Morton and others have pointed out the difficulty of securing satisfactory tissue for accurate diagnosis by biopsy at the time of operation because of the extensive inflammatory reaction. Although carcinoma can usually be excluded by careful inspection of the entire mucosa after the involved segment has been completely opened, to do this before removing the bowel introduces a serious risk of contamination. On the other hand, there is a serious objection to preserving the inferior mesenteric artery if there is a strong suspicion that carcinoma may be present. To divide the mesentery so as to preserve the inferior mesenteric and superior hemorrhoidal arteries in a patient with carcinoma seriously jeopardizes the en bloc nature of a good cancer operation even though the remaining mesentery and associated lymphatics are subsequently removed. For this reason Morton has advised that when carcinoma cannot be excluded, all of the mat-

ted tissue should be taken out in one block and a radical resection done just as for a definite carcinoma. In the presence of extensive inflammatory reaction, however, this procedure involves an extensive dissection, isolation of the left ureter throughout its course, the mobilization and lowering of the splenic flexure, and appreciably increases the operative risk.

It is obvious, therefore, that any evidence which will aid in making a presumptive diagnosis of either diverticulitis or carcinoma of the colon will be of value to the diagnostician and to the abdominal surgeon. With this problem in mind we have carefully reviewed the clinical records of 50 patients with severe diverticulitis seen at the clinic during the last 5 years. In each of these patients the disease process was sufficiently extensive as to make resection of the involved colon necessary. These cases were compared in detail with the records of 50 consecutive patients with carcinoma of the sigmoid or rectosigmoid seen during this same period. No patient was included in this group in whom a definite diagnosis could be established by digital or by proctoscopic examination.

Fig. 1. Barium enema film of a patient with diverticulitis of the sigmoid. The short length of the defect and the absence of mucosal folds at that point, with some suggestion of lipping, made it impossible to rule out carcinoma.

CLINICAL ANALYSIS OF CASES

The average age of the patients with diverticulitis was 53.5 years. The oldest patient was 74 and the youngest 34 years of age. The average age of the patients with carcinoma was 61.7 years. The oldest patient with carcinoma was 79 and the youngest was 36 years of age.

The incidence of diverticulitis was significantly higher in the male than in the female in this series; 31 or 62 per cent were males and 19 or 38 per cent were females. The sex incidence was approximately equal in the patients with carcinoma; 23 or 46 per cent were males and 27 or 54 per cent were females.

The incidence of nausea and vomiting was appreciably higher in patients with diverticulitis than in those with carcinoma; 54 per cent of patients with diverticulitis had either nausea or vomiting or both, whereas only 28 per cent of the patients with carcinoma of the sigmoid had either nausea or vomiting.

The incidence of abdominal pain was also significantly higher in patients with diverticulitis. Thirty-seven or 74 per cent of patients with diverticulitis complained of constant lower abdominal pain or distress, whereas only 13 or 26 per cent of patients with carcinoma complained of lower abdominal pain or distress. The incidence of pain of a colic-like nature was also significantly higher in patients with diverticulitis. Forty or 80 per cent of patients with diverticulitis had pain of this type, whereas only 19 or 38 per cent of patients with carcinoma complained of colic-like, lower abdominal pain. Thirty-eight per cent of patients with diverticulitis gave a history of chills and fever. Only 14 per cent of patients with carcinoma gave such a history.

Constipation, on the other hand, was a more frequent symptom in those patients with carcinoma. It was found in 26 or 52 per cent of patients with malignant tumors and in only 17 or 34 per cent of those with diverticulitis. Rectal bleeding was also much more common in patients with carcinoma. Thirty-two or 64 per cent of those patients with malignant lesions gave a history of having passed blood by rectum, while only 11 or 22 per cent of

Fig. 2. Barium enema film of a patient with carcinoma of the sigmoid, showing a sharply defined lesion with well demonstrated lipping of the margins of the defect, and destruction of the mucosal folds, with no evidence of irritability of the bowel wall.

patients with diverticulitis gave a history of rectal bleeding. Diverticulitis has been reported as occasionally giving rise to massive bleeding from the bowel. This is most unusual in our experience and no instances of severe bleeding were found in this series. No case of severe bleeding was found in the group with carcinoma. The incidence of diarrhea was exactly the same in both the malignant and the nonmalignant groups (28 per cent).

The two groups showed a marked difference in duration of symptoms. The average duration of symptoms in the patients with diverticulitis was 40.2 months, or over 3 years. Many patients with diverticulitis gave a history of symptoms of several years' duration. On the other hand, it is interesting to note that 1 patient with diverticulitis had symptoms for only 2 days before obstruction occurred. Another patient with diverticulitis had a perforation of his colon after only 4 days of abdominal symptoms, another 6 days, and still another, 7 days. In all of these patients obstruction or abscess formation developed from diverticulitis which had been asymptomatic up to that time. The patients with carcinoma had an average duration of symptoms of 8.5 months; the shortest duration of symptoms was 3 days and the longest was 4 years. The patient who had had symptoms for 4 years had diverticulitis in addition to carcinoma. No patient who had carcinoma alone had symptoms for longer than 2 years.

Six or 12 per cent of patients with diverticulitis had a palpable abdominal mass which could be felt through the rectal wall. Eight or 16 per cent of the patients with carcinoma had a palpable abdominal mass. In 3 patients with carcinoma of the sigmoid, a pelvic mass could be felt through the rectal wall. Although abdominal tenderness was present in 13 or 26 per cent of patients with diverticulitis, it was also present in 8 or 16 per cent of the patients with carcinoma. In addition to abdominal tenderness, 8 patients with diverticulitis had rectal tenderness and no patient with malignant disease had rectal tenderness.

Laboratory data were of little help in distinguishing diverticulitis from carcinoma. The average estimation of hemoglobin in the patients with diverticulitis was 13.8 grams; in those with carcinoma it was 13.2 grams. The average white blood cell count in patients with diverticulitis was 8,700; in patients with carcinoma it was 9,100.

The proctoscopic examination in all of the patients with carcinoma included in this series was negative, as previously pointed out. Of the patients with diverticulitis, suggestive evidence was found on proctoscopic examination in 8 or 14 per cent. This consisted of edema of the rectal wall, fixation of the rectosigmoid and marked spasm. In 1 patient a colovaginal fistula due to diverticulitis was found on proctoscopic examination. Proctoscopy in the remaining 41 patients with diverticulitis was negative.

On barium enema examination a definite diagnosis of diverticulitis was made in 29 or 58 per cent of the patients. In an additional 7 or 14 per cent, a probable diagnosis of diverticulitis was made, usually based on signs of perforation or fistula formation. In 8 or 16 per cent, it was impossible to distinguish between carcinoma and diverticulitis on barium enema study. Of the patients with diverticulitis 11 or 22 per cent had a marked degree of obstruction and 5 or 10 per cent had complete obstruction of the colon. Of the patients with carcinoma it was possible to make a definite diagnosis on barium enema study in 38 or 76

Fig. 3. Barium enema film of a patient with diverticulitis of the sigmoid. A long segment of bowel is involved; there is preservation of the mucosal folds in the center of the defect; the constricted ends are somewhat cone-shaped, and there is evidence of irritability, as shown by the "saw teeth."

Fig. 4. Barium enema film showing complete obstruction of the rectosigmoid which could have been produced by either carcinoma or diverticulitis. The roentgenologic diagnosis in this case was carcinoma of the rectosigmoid. At the time of operation, the patient was found to have diverticulitis.

per cent. In 7 or 14 per cent of patients with carcinoma a diagnosis of probable carcinoma was made on barium enema study but because of diverticula and spasm, diverticulitis could not be ruled out. In 2 patients it was impossible for the roentgenologist to say which of these two conditions was present (Fig. 1). It is of interest to note that no patient with carcinoma showed definite evidence of perforation of the colon on barium enema study. In 5 patients with carcinoma the barium enema study revealed a marked degree of obstruction and 1 patient had complete obstruction.

Twenty or 40 per cent of those patients with diverticulitis were found at operation to have a perforation with abscess formation, 22 per cent had significant degrees of obstruction of the large bowel and in 17 or 34 per cent the obstruction was associated with a fistula. Fourteen per cent had a colocutaneous fistula, 10 per cent a colovesical fistula, 8 per cent a coloileal fistula, and 2 per cent a colovaginal fistula. Of the patients with carcinoma, 8 or 16 per cent were found at operation to have a marked degree of obstruction. Three patients with carcinoma had a perforated lesion and 1 patient had a sigmoidovesical fistula at operation.

All of the clinical material is summarized in Tables II and III.

DISCUSSION

As is well known, there is no significant difference in the age incidence of patients with carcinoma and those with diverticulitis of the colon, although the average age of the patients in this group with diverticulitis was 8 years younger than those with carcinoma. The sex incidence is also similar in the two groups although in the present series 62 per cent of the patients with diverticulitis were males as compared to 46 per cent in the group with carcinoma.

The incidence of abdominal pain was significantly higher in the patients with diverticulitis (74 per cent) than in those with carcinoma (26 per cent). The incidence of colic-like pain was also significantly higher in the patients with diverticulitis, 80 per cent, as compared to the patients with carcinoma, 38 per cent.

The incidence of rectal bleeding, on the other hand, was significantly higher in the patients with carcinoma (64 per cent) as compared to the group with diverticulitis (22 per cent). Two of the 11 patients with diverticulitis and rectal bleeding had associated mucosal polyps and several had large internal hemorrhoids, which may have been responsible for the bleeding in these cases.

Nausea and vomiting, and chills and fever were more frequently found in patients with

TABLE II. — SYMPTOMS

Complaint	Carcinoma		Diverticulitis	
	No.	Per cent	No.	Per cent
Nausea and vomiting	14	28	27	54
Diarrhea	14	28	14	28
Constipation	26	52	17	34
Colicky abdominal pain	19	38	40	80
Blood by rectum	32	64	11	22
Abdominal pain	13	26	37	74
Rectal pain	2	4	5	10
Fever and chills	7	14	19	38
Abdominal masses	8	16	6	12
Rectal masses	3	6	6	12
Abdominal tenderness	8	16	13	26
Rectal tenderness	0	0	8	16

diverticulitis, and constipation was more frequent in patients with carcinoma. As might be expected, the average duration of symptoms was appreciably longer in patients with diverticulitis than in those with carcinoma, although several patients with diverticulitis had had symptoms for less than 1 week. On physical examination the incidence of an abdominal or a pelvic mass felt by rectum was the same in both groups, although abdominal or rectal tenderness was more common in patients with diverticulitis.

Laboratory data, such as the hemoglobin or white blood cell count, were of no help in distinguishing between carcinoma and diverticulitis in this study. Proctoscopic examination was of little help in distinguishing between carcinoma and diverticulitis when the malignant lesion could not actually be visualized. Eight or 16 per cent of the patients with diverticulitis presented signs of an inflammatory lesion at the rectosigmoidal level. This, of course, does not rule out carcinoma.

TABLE III. — OPERATIVE FINDINGS

	Carcinoma		Diverticulitis	
	No.	Per cent	No.	Per cent
Perforation and abscess	3	6	20	40
Obstruction	8	16	11	22
Fistula	1	2	17	34

Roentgenographic study by means of the barium enema examination has long been the chief means of distinguishing between carcinoma and diverticulitis of the sigmoid colon. If the lesion is typical of malignant disease, as it was in 76 per cent of the patients with carcinoma, a sharply demarcated defect is present with complete loss of mucosal markings and frequently a characteristic lipping of the edges of the defect (Fig. 2). In patients who present a longer defect, frequently with preservation of some of the mucosal markings and evidences of marked spasm or irritability as indicated by the saw-tooth or picket fence appearance of the barium outline, a definite diagnosis of diverticulitis can often be made (Fig. 3). This was possible in 58 per cent of the group with diverticulitis. In addition, 14 per cent of patients with diverticulitis showed evidences of perforation and fistula formation, and a presumptive diagnosis of diverticulitis could be made. None of the patients with carcinoma showed evidence of perforation or fistula formation on barium enema study. There remains, however, a significant number of patients in each group in whom a definite diagnosis of carcinoma or of diverticulitis could not be made by barium enema study. Nine or 18 per cent of the patients with carcinoma presented some evidence of diverticulitis on barium enema study, and in 8 or 16 per cent of patients with diverticulitis, carcinoma could not be excluded by the barium enema. In addition, 10 per cent of the patients with diverticulitis and 1 patient in the group with carcinoma were found on barium enema examination to have complete obstruction, and the length and character of the defect could not be determined (Fig. 4).

A review of the operative findings indicates the difficulty which frequently exists in distinguishing between carcinoma and diverticulitis, even when the process is exposed at the time of operation. An equal number of patients in the malignant and nonmalignant groups showed evidences of partial obstruction to the colon caused by a firm, hard mass in the sigmoid and rectosigmoid. Advanced carcinoma of the sigmoid is frequently associated with a marked inflammatory reaction in the surrounding peritoneum and retroperi-

toneal tissues. A significantly higher number of patients with diverticulitis had actual perforation with abscess formation (40 per cent) than did patients with carcinoma (6 per cent), and 34 per cent of the patients with diverticulitis showed evidences of fistulous formation between the colon and the vagina or between the colon and the bladder or small bowel. Only 1 patient in the group with carcinoma was found to have a fistula and that was between the colon and bladder.

SUMMARY AND CONCLUSIONS

The differential diagnosis between carcinoma and diverticulitis of the colon may at times be difficult. Both conditions occur in patients of the same age group and both affect most frequently the same segment of the colon. Each condition is frequently associated with varying degrees of obstruction of the colon and may present an identical clinical picture. Although roentgenologic study will establish the diagnosis in the majority of patients, there will always be an appreciable number of patients in whom a definite diagnosis of either diverticulitis or carcinoma cannot be made on barium enema examination. It is in this group that a careful review of the history may help to establish a presumptive diagnosis of either carcinoma or diverticulitis. This is of definite practical value to the surgeon called on to operate on these patients.

Certain characteristic differences have been pointed out in the symptomatology of a group of 50 consecutive patients who required resection of the sigmoid colon because of diverticulitis, and a group of 50 consecutive patients in whom the lesion in the sigmoid was found to be carcinoma.

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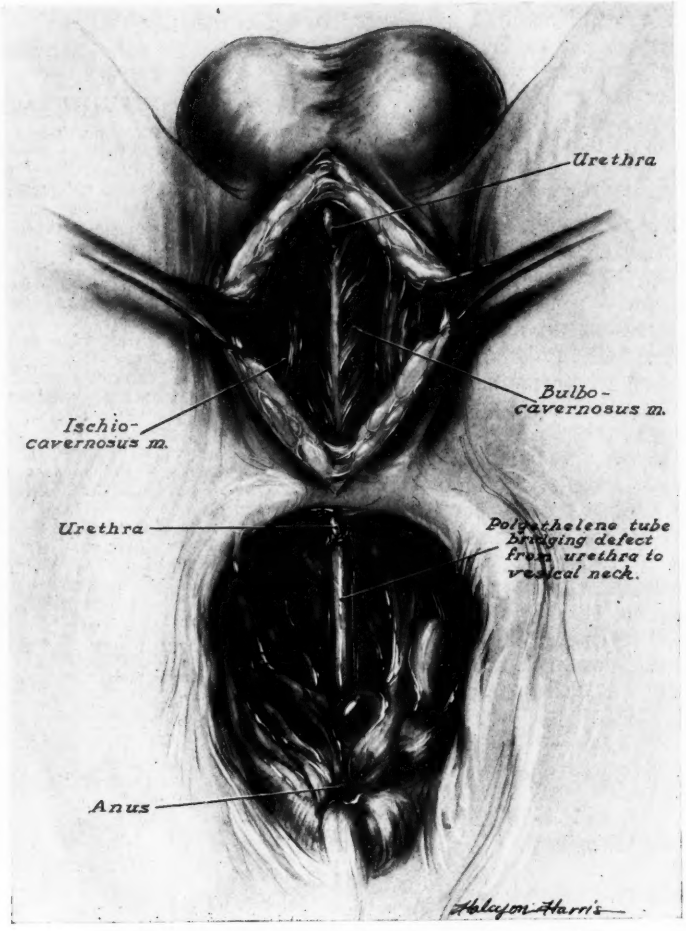

Fig. 4. Appearance of perineum; incision over bulbous urethra.

Reconstruction of Posterior Portion of Urethra.—Henry M. Weyrauch and Ranulf P. Beames.

RECONSTRUCTION OF POSTERIOR PORTION OF URETHRA

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IF CONSIDERABLE tissue has been lost, repair of the injured posterior portion of the urethra constitutes a serious operative problem. In our experience the usual methods of (1) free transplantation of skin or vein or (2) utilization of a flap of bladder have proved unsatisfactory. Transplants frequently slough and give rise to stricture formation. Urinary incontinence is an unavoidable complication of the bladder flap operation since the external urinary sphincter is usually damaged and construction of a flap from the bladder destroys the internal sphincter.

This report concerns the successful application of the English pull-through procedure to replace the posterior urethra.

The pull-through operation of Badenoch was devised for the surgical correction of impermeable urethral stricture. Following excision of the strictured segment of the bulbomembranous urethra, the distal portion of the bulb is extensively mobilized and, by means of a pull-through maneuver, is used to replace the defect.

Although somewhat similar to procedures of Watson (Fig. 1), making use of a lateral flap and of Wells (Fig. 2), incorporating an anterior urethral flap, the advantages of using the entire urethra to replace the defect are evident; the defect is bridged by a completely epithelialized channel, it is well vascularized and not likely to slough or give rise to stricture formation—hazards inherent in elongated flaps of urethra.

Badenoch's procedure was closely followed in the case herewith reported.

CASE REPORT

A 16 year old white male entered Stanford University Hospitals 6 hours after sustaining an extensive gunshot wound of the perineum, produced by a 16 gauge shotgun at a distance of 4 feet. On entry, the patient exhibited the characteristic signs of shock. His pulse was 140 and the blood pressure 80/40. A transfusion of 2 units of whole blood was given and antibacterial therapy was initiated.

Nine hours after the accident careful examination and débridement of the wound was carried out under general anesthesia. The rectal mucosa was intact, but separated from the sphincter muscles and associated perineal structures. The prostate hung loosely in the wound, connected to the vesical neck by the merest shred of connective tissue. The most proximal portion of the bulbomembranous

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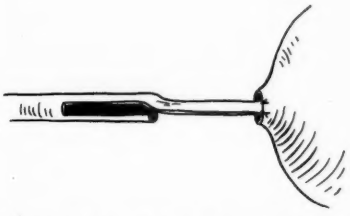

Fig. 1. Lateral flap of urethra constructed by Watson's method.

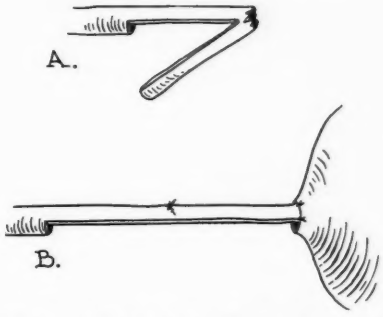

Fig. 2. Anterior flap of urethra constructed by Wells' method.

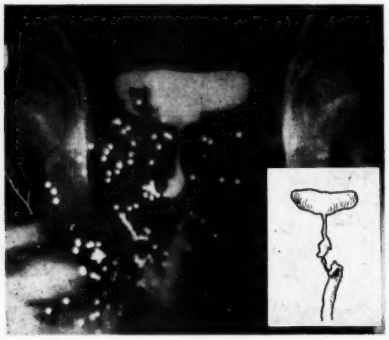

Fig. 3. Preoperative cystourethrogram showing long sinus tract from end of divided bulbous urethra to bladder. Numerous shot remain in perineal tissues.

urethra was absent, and no part of the urogenital diaphragm could be identified. Blood clots and innumerable 3 millimeter size shot were removed, and devitalized remnants of tissue, including the entire prostate, were débrided. Suprapubic cystostomy was next carried out. A large hematoma was found in the space of Retzius. The wall of the bladder was intact, although several shot were present in the wall, in the perivesical tissues, and within the cavity of the bladder. A No. 22F Robinson catheter was passed through the penile urethra across the perineal defect and into the bladder. A No. 30F mushroom catheter was left in place as a cystostomy tube. A sigmoid colostomy was also performed.

On the thirteenth postoperative day the perineal wound was re-explored and again débrided. It was observed that the entire posterior urethra and a small portion of the bulbous urethra were lacking. A polyethylene tube was substituted for the urethral catheter. During the next few weeks, fresh granulations formed, but it was obvious that there was no growth between the severed urethral segment and the vesical neck. A cystourethrogram showed a long sinus tract from the divided bulbous urethra to the bladder (Fig. 3). The decision was made to carry out Badenoch's procedure, the operation being performed 4 months following injury.

With the patient in the extreme lithotomy position, an incision was made over the bulbous urethra (Fig. 4) and the edges of the skin

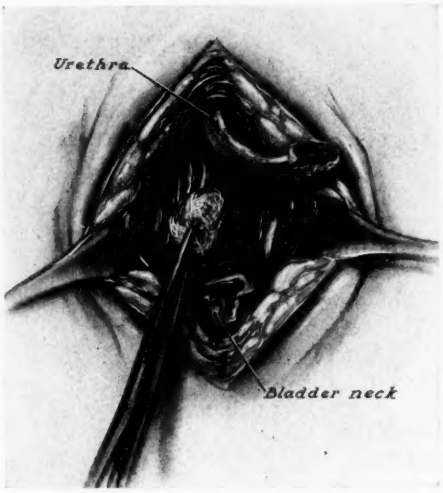

Fig. 5. Wide mobilization of bulbous urethra and freeing vesical neck to permit approximation.

around the granulating area were elevated. The bulbous urethra was freed for a distance of 6 centimeters (Fig. 5). It is surprising how readily this structure can be isolated and how elastic it is. Sufficient mobility was developed to bridge the defect without tension on the urethra. Active bleeding at the end of the bulbous urethra indicated the excellence of the blood supply. The vesical neck was freed and prepared for anastomosis by coning out granulations with a scalpel, taking care to avoid damage to the internal sphincter. A No. 24 Robinson catheter was introduced through the penile urethra. After the bulbous urethra was fixed to the catheter with a few interrupted sutures of No. oo chromic catgut, the end of the catheter was introduced through the vesical neck and brought out through the existing cystotomy (Fig. 6). It was fixed in this position by a hemostat applied at the abdominal wall and the end of the bulbous urethra was sutured to the vesical neck by 4 interrupted sutures of No. oo chromic catgut. In addition to the urethral catheter a No. 22 Malecot catheter was left in place as a cystotomy tube. The subcutaneous tissues of the perineum were brought together over the elongated bulbous urethra, the skin was closed, and a Penrose drain left in place.

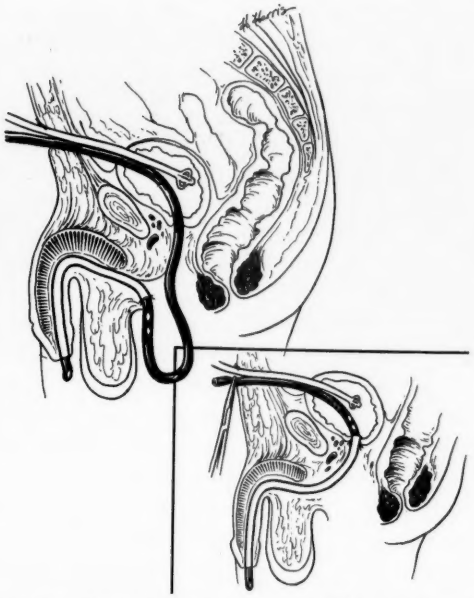

Fig. 6. Distal urethra sutured to urethral catheter which serves as splint. Catheter brought out suprapubically, held in position by clamp at abdominal wall, and anastomosis at vesical neck.

The patient's convalescence was uneventful. On the fifteenth postoperative day, the Malecot suprapubic catheter was removed and, on the twenty-fifth postoperative day the urethral catheter was found to be free and was removed. For 2 days the patient was completely incontinent. On the third day he was able to retain 300 cubic centimeters of urine in his bladder with effort. At examination 5 months after operation the perineal and suprapubic wounds were completely healed, and there was no evidence of urinary infection. The patient exercised absolute control over a urinary stream of large caliber, indicating normal function of the internal sphincter. A cystourethrogram showed a urethral channel of wide patency (Fig. 7).

The patient returned 1 year later for reconstruction of the anal sphincter and closure of the colostomy, following which he developed normal bowel control. The only functional impairment is an inability to attain more than partial penile erections since the accident.

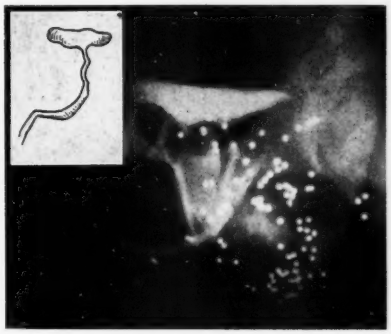

Fig. 7. Cystourethrograms taken 5 months following operation showing urethral channel of normal caliber.

SUMMARY

The Badenoch pull-through operation is ideally suited to repair extensive injury of the bulbous and posterior urethra. Since absence of long segments precludes any simple form of anastomosis, the procedure is likewise useful following excision of extensive stricture and malignant disease of this portion of the urethra.

In utilizing the entire circumference of the urethra to bridge the defect, and in approximating undamaged tissues, the pull-through operation avoids slough and stricture formation. Since the external sphincter is no longer present, the ability of a patient to exercise urinary sphincter control following this procedure depends solely on the competence of the internal sphincter.

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EDITORIAL

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THE PROBLEM OF THE FRACTURED HIP

IN HIS book *Dislocations and Fractures of the Joints* published a little over 100 years ago, Sir Astley Cooper states the following: "In the examinations which I have made of transverse fractures of the cervix femoris I have met only one in which bony union had taken place or which would not admit of motion of one bone upon the other." This statement, happily, is not true at present although all with fracture experience believe that the results today in the intracapsular type of femoral fracture leave much to be desired and we will doubtless agree with Kellogg Speed who called this in 1935 "the unsolved fracture."

A distinct departure from the splinting and traction methods in vogue during Cooper's time was introduced about 1875 by Lucas-Championniere, who was an uncompromising advocate for movement in the treatment of all conditions resulting from injury. Speaking of fractures of the hip, he advocated that the day after the fracture the patient should be moved from the bed to the chair and shortly thereafter should be encouraged to put his foot on the floor. After stressing his method of early active movement, he states very cannily that his results in fracture of the hip compare favorably with those obtained by other methods in vogue, no better, no worse.

Wharton Hood in his textbook on the *Treatment of Injuries* published in 1902 states that "union of the fracture of the neck of the femur never occurs and it is useless to endeavor to obtain it." Accurate reduction or bony union of this fracture was not the generally recognized aim or even expectation of surgeons even at the beginning of this century.

Royal Whitman, about 1890, began teaching that the restoration of function following fracture of the neck of the femur was dependent upon its anatomic reduction and he believed that the primary essential to functional repair was restoration of the femoral angle. He achieved this by insisting upon *accurate reduction*, pointing out that the limb should then be placed in a plaster spica in full abduction, internal rotation, and full extension. This procedure impinges the greater trochanter against the ilium and causes the Bigelow ligament, under the inferior border of the neck, to become tense, thereby holding the reduced fragments in a vise and assuring firm fixation. A great deal of opposition to this method followed, but it must be admitted that many of those opposed to it were unfamiliar with the principles of the method as well as the pitfalls of plaster of Paris technique. Whatever valid objections may be advanced against the widespread use of this method, Whitman must certainly be given

credit for being the exponent of a radical reform in the treatment of this type of fracture.

For many years various types of wood screws were employed unsuccessfully, but in 1915 Albee described the tibial bone graft for treatment of fresh fractures of the hip. In 1931 Smith-Petersen introduced the three flanged nail; Johansson followed a year later with his cannulated nail. These pioneers introduced an effective method of *internally* splinting the fracture. In addition, internal fixation made possible early movement of the hip which was impossible with the Whitman abduction method. It also permitted massage and early, active mobilization of the limb—essential features in all fracture treatment which had been so vigorously and persistently fought for by Lucas-Championniere even though he had given little or no attention to accurate reduction.

For the past 25 years, at least, emphasis has been placed on accurate reduction combined with some type of internal fixation. All kinds of ingenious metal agents, as well as autogenous and heterogeneous grafts have been used.

Factors producing nonunion. A. The upper end of the femur possesses certain fundamental anatomic peculiarities which are of considerable importance in a discussion of intracapsular fracture. The joint is a weight-bearing one, yet the weight is normally not borne directly on the long axis of the bone but obliquely through the head and neck. Therefore, while accurate anatomic reposition of any fracture is desirable, in this type of fracture it is even more so if the best opportunity for bony union is to be given. It should be mentioned that while a coxa valga reduction (the abduction type of Watson-Jones) will often give a satisfactory result, the coxa vara position (the adduction type) almost always gives a poor result because it introduces at the fracture site many mechanical factors that tend to displace the fragments, such as shearing stresses and strains.

B. Apart from the unusual bony conformation, the inadequacy of the blood supply has long been advanced as a factor in the development of nonunion in this fracture. In adults the main blood supply is received through the inferior and superior visceral capsular vessels entering the head near the epiphyseal plate region. The base of the neck region is supplied also through the nutrient artery of the femoral shaft.

A great controversy has centered about the importance of the ligamentum teres. Many anatomists regard it as a useless, avascular structure, while a number have reported that it normally possesses blood vessels supplying the head of the femur. Wolcott in 1943 published interesting results and found that "In approximately 20 per cent of adults if the ligamentum teres is injected successfully the vessels fail to enter the head." All of this work was done on autopsy specimens and few observations are found on the patency of these vessels in the living patient. Albee stated that he had removed 174 femoral heads and in only 1 instance did he note bleeding of any consequence in the stump of the ligamentum teres. It would seem quite likely that the vessels that are normally present may often be seriously injured at the time of the initial fracture or during rotation of the head fragment in the acetabulum, and therefore, serve no longer as normally conducting blood vessels. In addition to this is Wolcott's statement that 1 adult out of every 5 normally does not receive blood into the head of the femur through the ligamentum teres. Only a few instances have been personally found in which bleeding of the ligamentum teres has been noted at the time of removal of the head during the course of a reconstruction operation.

In summarizing regarding the blood supply to the head and neck, it can be stated that the circulation to the caput and adjacent portion of the neck is not as extensive or plentiful as that to the base of the neck and the greater trochanter area. This is another way of expressing the old adage that "The nearer the fracture approaches the head the poorer the prognosis for bony union, and the nearer the base of the neck the better the prognosis."

C. Another cause of nonunion is the interposition of soft tissue between the fragments. We have noticed a number of times that those cases which are difficult to reduce by closed reduction may at open operation disclose a curtain of capsule, which has become wedged between the bony fragments, preventing accurate reduction. Magnuson has described and illustrated very graphically the variety of fractures that can occur within the hip joint capsule, pointing out the difficulty that might be anticipated in obtaining reduction in some of these oblique and transverse fractures. Many surgeons have become very adept at closed reduction and the blind insertion of some form of internal fixation, but Magnuson's work as well as personal experience inclines us to believe that at times blind nailing can be very deceptive.

Other complications. Along with the development of nonunion there will be varying degrees of bone absorption and aseptic necrosis of the head fragment. These are two very interesting phenomena and their subsequent development can occasionally be prophesied at the time of the original reduction. Aseptic necrosis may develop both in patients after union has occurred and in those with nonunion. One may see very rapid bone absorption in even as short a period as 4 weeks, but after fracture usually several months will elapse before changes are evident in the roentgenogram. In 1930 Santos published a very important paper emphasizing the fact that when the roentgenogram discloses a sclerotic head the indication is that it is the seat of an aseptic necrosis. If this necrosis is extensive it means that the head is no longer viable and may need removal. When it is not sclerotic or only slightly so, it may become revascularized by what Phemister has called "creeping substitution."

Another finding in the roentgen picture is a narrowing joint space, indicating that some degree of absorption of the cartilaginous articular surface of the head and acetabulum is beginning and later this will seriously interfere with hip function.

The mortality statistics, considering the age and debility of the majority of these patients, are not thought to be any higher than would be noted in other fractures in the same age group. In 1927 Lofberg reported 264 cases treated by the Whitman method with a mortality rate of 6 per cent; 67.5 per cent of his cases presented bony union. Whitman refers to 441 patients with intracapsular fracture in which 126 were over 70 years of age and 57 were over 80 years of age, with a mortality of 7 per cent. The Fracture Committee sponsored by the American Academy of Orthopaedic Surgeons in 1939 made a report on 1,485 intracapsular fractures with a mortality of 8 per cent, and in 1941 reported a mortality rate of 11.6 per cent in a total of 923 cases treated by internal fixation.

In considering the question of bony union in 241 cases, this Committee found those patients with Smith-Petersen nailing obtained bony union in 72.9 per cent. The immediate results were greatly improved by the use of internal fixation, but they stressed the fact that in the hands of the ill trained, the results are often deplorable and much inferior to those which are seen following nonoperative methods.

In the cases of internal fixation there was a large percentage exhibiting either early or late aseptic necrosis or varying degrees of arthritis of the hip joint. In the 241 cases mentioned, 51.8 per cent exhibited some arthritic change. Boyd reports that about a third of 300 patients developed aseptic necrosis and a third some degree of arthritic change; hence he classified only 43.6 per cent as representative of a good result although bony union occurred in 86.5 per cent of his series.

In these combined series of cases, totaling over 3,000 patients with intracapsular fracture, the mortality rate has ranged from 6 to 11.6 per cent, the mortality being consistently lower in cases treated by nonoperative methods. The percentage of bony union, on the other hand, has steadily increased following the use of internal fixation, although an increased number of late complications have been reported, especially aseptic necrosis and arthritis. Whether these have been due to the presence of metal fixation in the tissue or to some technical error accompanying the use of wires, pins, and screws is still an unanswered question.

In summary, the intracapsular fracture of the hip occurs primarily in the elderly patient and is still the one to be feared most by them. Because of its frequent occurrence in the ebb tide of life and because careful follow-up statistics show a high percentage of disabling sequellae, it behooves the surgeon today to give a cautious prognosis regarding the restoration of normal function. A great deal of progress has been made in lowering the mortality rate and in obtaining bony union, but aseptic necrosis of the head and degenerative arthritic changes still occur all too frequently.

PAUL C. COLONNA.

THE SURGEON AT WORK

A SIMPLIFIED, INEXPENSIVE TECHNIQUE IN HYSTEROSALPINGOGRAPHY

ARTHUR J. BENDICK, M.D., New York, New York

FOR over 25 years I have been interested in studying the physiology and pathology of the female genital tract by means of metrosalpingography. My earlier observations were made with I. C. Rubin and at that time we used lipiodol as the opaque medium. Together we reported observations on the tubal peristalsis and the value of uterotubal roentgenograms (3, 4, 5).

Since that date hundreds of thousands of cases have been examined by different observers. The opaque material has varied with different people, and the type of examination has also changed considerably.

Lipiodol is still one of the best of the opaque media and is still the best when the examination is made for determining the cause of sterility. For studying uterine pathology, it has been almost completely superseded by the aqueous absorbable materials such as rayopake, medopaque, and many others. The reason lipiodol is necessary in the study of sterility is that at present it is the only medium that can be visualized out in the peritoneal cavity several hours after it has passed out of the fimbria. If a tube is subject to spastic constriction or is partially but not completely occluded pregnancy may still result and a film, taken the morning after the examination, showing lipiodol in the peritoneal cavity indicates that these women can become pregnant. Absorbable media cannot be used if a film to test tubal patency is desired the following morning.

Lipiodol, however, has the distinct disadvantage of not being absorbed and remains as a persistent shadow either in the peritoneal cavity or in an occluded tube. I have given up the use of lipiodol completely when interest is centered only on uterine or tubal pathology in which the cause of sterility is not important.

In studying uterine pathology, the water soluble media have a further advantage inasmuch as they are not as opaque as lipiodol; therefore, small polypoid masses can be seen as translucent shadows within the uterine cavity much more readily than with more opaque media. Both rayopake and medopaque have another advantage in that they usually give a better coating of the uterine mucosa, especially when the solution is withdrawn and air injected.

During the past years, two types of examinations quite different from each other have developed in the study of the uterus and tubes by metrosalpingography. The first school, to which I belong, always controls the injection by fluoroscopy. The position of the cannula is checked by fluoroscopy before any media is injected. The injection is done completely under fluoroscopic control, and films are taken at various stages of uterine filling. By far the majority of physicians prefer fluoroscopic control.

In recent years a different type of examination has been instituted. In this method the patient is placed on a Bucky table just as for a retrograde pyelogram. After the cannula is inserted, 1.0 cubic centimeter of the opaque solution is injected and a 10 by 12 inch film is taken. Successive films are taken after each cubic centimeter of injection. No fluoroscopy is used. The films taken by this method have good quality inasmuch as they are all taken on a Bucky diaphragm. Only one physician is required for this examination.

In the many hundreds of women whom I have examined I have always had a gynecologist do the instrumentation while I did the fluoroscopy and spot filming of the patient. Inasmuch as I believe that this examination should represent teamwork between gynecologist and radiologist, the fact that two physicians are needed is no disadvantage.

With the fluoroscopic method, it is not necessary to measure the amount that is injected, since it is always controlled by fluoroscopy. As soon as the first trace of opaque solution is seen within the uterine cavity, the first spot film is taken. As more of the fluid is injected, additional exposures are made until the uterine cavity is completely outlined. It has been my custom then to stop the

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fluoroscopy and to take one or two films with the overhead tube. The fluid from the uterine cavity is then withdrawn, the instruments are removed, and another film is taken. Additional films are taken depending upon what information is desired and what pathologic change has so far been demonstrated. With carefully controlled fluoroscopic spot films of the partial filling, the use of air after withdrawal of the fluid is not as important as before this type of examination, but at times is still indicated.

At present, uterosalpingography is becoming a very frequent type of examination. In attempting to reduce the cost of the examination as well as to simplify the technique, I have devised a very simple procedure which is now uniformly carried out in my office and hospitals.

All well equipped hospitals have fluoroscopic tables equipped with spot devices, the majority having what we radiologists call a four exposure spot device which permits a single 8 by 10 inch film to have four exposures made on it, each occupying only one-quarter of the film. The mechanism may be either hand or motor driven.

The patient is placed on the fluoroscopic table. The gynecologist inserts the speculum, sterilizes the external os, grasps the os with a tenaculum, and inserts the cannula to which the syringe containing the opaque medium has been added. It is very important that there are no air bubbles in either the syringe or cannula. The cannula and syringe are held erect and the solution is injected until a drop of the solution comes out from the tip of the cannula. This method eliminates all possibility of air within the cannula or syringe which may cause a translucent shadow simulating a small polyp. It is a simple procedure but is very important for an accurate examination. The patient's legs are then extended, and before any injection is made the radiologist begins the fluoroscopy. It is important for the radiologist to be sufficiently dark adapted by wearing fluoroscopic goggles for the required time prior to the fluoroscopy so that from the positions of the speculum and the tip of the cannula he can readily tell if the tip is within the uterine cavity. He then instructs the gynecologist to inject a very small amount. As soon as some is seen to enter the uterine cavity, the first spot film is taken. Small additional amounts are then injected until all four of the spot exposures have been taken. Each partial injection is checked under fluoroscopic control, the injection being made while the radiologist is making the fluoroscopic examination. With this technique the four stages of filling the uterine cavity are obtained on one 8 by 10 inch film.

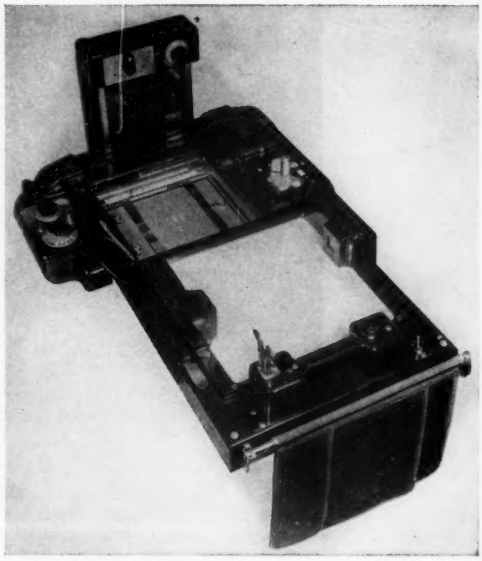

Fig. 1. Typical fluoroscopic screen equipped with four-in-one spot film device.

It has been my custom then to take one 8 by 10 inch spot film of the uterus and the tubes while the instruments are all in position and the uterine cavity is still full.

It is surprising to note how much information is obtained concerning the anatomy, physiology, and pathology of the genital tract on these simple two 8 by 10 inch films. In the vast majority of cases most of the information that is necessary can be obtained from this part of the examination without supplementing it with any other films. When expense is important and large numbers are being examined routinely, the examination may end after these two films have been taken. In my private practice I have usually supplemented them with overhead films taken on the Bucky diaphragm: one 10 by 12 inch film being taken while the instruments are in position, one after aspiration of the opaque material, and one about a half hour later after the instruments have been withdrawn. Another simple way in obtaining additional information is after the spot film has been taken of the entire genital tract, the four-in-one spot device is again used in the reverse order as the gynecologist withdraws the fluid. This procedure also gives a very excellent visualization of the uterine cavity.

Inasmuch as throughout the entire country there are thousands of patients being examined by

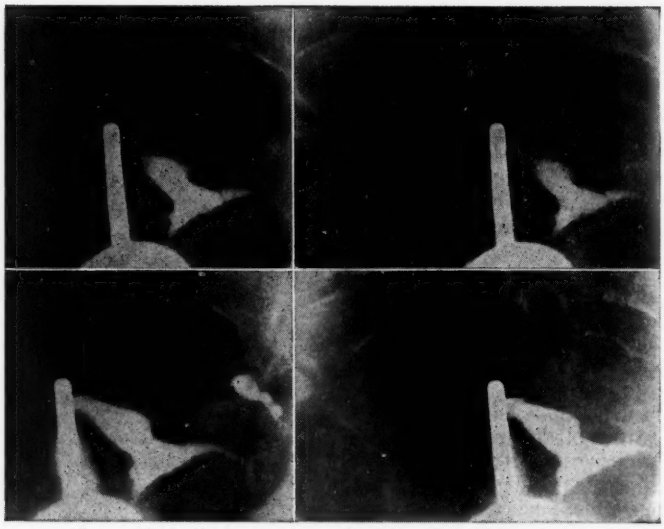

Fig. 2. Markedly flexed uterus with hyperplasia of the mucosa.

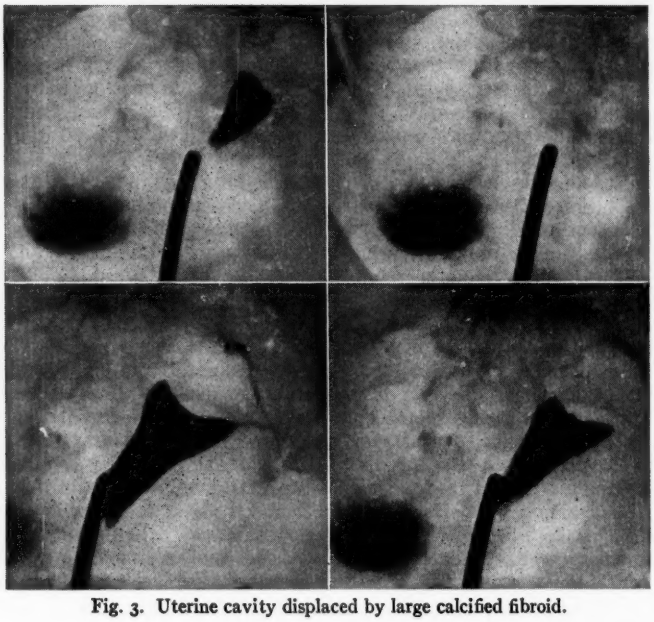

Fig. 3. Uterine cavity displaced by large calcified fibroid.

the fluoroscopic method and by the direct film method without fluoroscopy, I think it is advisable to compare their merits and disadvantages.

The advantages of the fluoroscopic control method are many. It is difficult to state beforehand without visualizing the lumen just how much opaque solution is necessary to fill the uterine cavity completely: 3.0 cubic centimeters may be sufficient but, on the other hand, at times as much as 10.0 cubic centimeters have been neces-

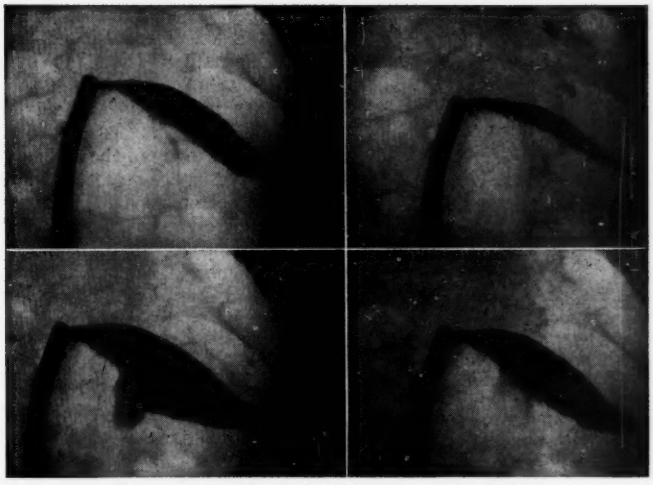

Fig. 4. Large uterine cavity showing marked flexion.

Fig. 5. Uterine cavity enlarged and displaced.

sary to outline the cavity completely. The injection of 10.0 cubic centimeters has no disadvantage as long as it is being fluoroscopically controlled and all the fluid is kept within the uterus. In the blind method a like injection is detrimental as some may be going out into the peritoneal cavity.

Another great advantage of the fluoroscopic method is that information is immediately available as to the size of the uterus, the amount of opaque solution that is within the uterine cavity, and whether any of the solution has passed out into the tubes. Films do not have to be developed to obtain this information, and the examination can, therefore, be quick and inexpensive. Another advantage is that it is far safer to the patient, inasmuch as a minimal amount of opaque solution will pass out into the peritoneal cavity. I have found both rayopake and medopaque to be irritating when they pass out into the peritoneal cavity in appreciable amounts.

Fig. 6. Uterine cavity showing marked hyperplasia due to neoplastic invasion.

The school that uses the direct film method without fluoroscopy claims that only one physician is necessary and that the apparatus is not as elaborate. A dark room for fluoroscopy is not necessary, and if the work is being performed by a gynecologist, the equipment is much less complicated. These arguments may apply in private practice, but they certainly do not apply in modern hospitals where all this equipment is available. Inasmuch as the fluoroscopic method is a well controlled and much safer procedure, I believe that it is the method of choice. The argument used by the other school that only one physician is necessary does not apply, inasmuch as the instrumentation should be done either by a gynecologist or in a hospital at least by the gynecologic resident. Better teamwork is obtained and the gynecologist certainly should know better just what information he desires.

This simplified method of fluoroscopic observation utilizing the four position spot device was elaborated in order to reduce the time of the examination and to cut the cost of the procedure. The four exposures on the four position spot device can be taken much faster than four films can be placed and removed in the Bucky tray. The entire fluoroscopic procedure should not take more than 2 or 3 minutes. No one can change four films in the Bucky tray and go back to the control booth in that time. Some gynecologists remain at the table during the entire injection while the technician changes the films. This method is so dangerous, exposing the gynecologist to so much radiation, that it should never be used.

Another advantage to the fluoroscopic method is that there is a saving to the hospital of between 8 and 10 dollars for this single part of the examination, since one 8 by 10 inch film is used instead of four 10 by 12 inch individual films. This method is faster, less expensive, more accurate and safer for the patient than the overhead film type examination.

Another disadvantage of the nonfluoroscopic method is that the examination is usually completed before any of the films are seen. If any additional films are required, the instruments have already been removed and later the patient must be completely re-examined. With the fluoroscopic control method, the information is immediate.

The gynecologist's hands are close to the field of radiation. In order to give adequate protection to his hands a sheet of heavy lead rubber should be placed on the table extending up to the woman's pubic bones. The radiologist, who should be better acquainted with the dangers of radiation, should check the position of the lead apron as soon as the fluoroscopy is started. The edge of the lead apron should be seen just below the cannula. The radiologist, who should know how to protect himself, need only wear a heavy lead apron; inasmuch as his hands do not have to be in the field the wearing of lead gloves is optional.

During the past years the value of teamwork between the gynecologist and the radiologist instead of solo work by either one has definitely demonstrated its superiority. Some gynecologists who have been doing numerous examinations of this type have already developed x-ray burns of their fingers, and at least one whom I know will probably lose one or two fingers. Today, more gynecologists, urologists, and dentists are developing x-ray burns than radiologists because, intent on their work, they have not been sufficiently cautioned against the continued use of x-ray.

Recently I have had occasion to perform this examination with gynecologists who have been using the fractional method in their offices, i.e., using only films without fluoroscopy. They have told me that after seeing the two types of examination, they are so convinced of the superiority of the fluoroscopic method that they will no longer use their method.

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THE TECHNIQUE OF SUBTOTAL GASTRECTOMY FOR DUODENAL ULCER (RADICAL DISTAL PARTIAL GASTRECTOMY)

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IN THE treatment of those cases of duodenal ulcer which require surgery, it has been shown that a radical partial gastrectomy gives the best results. In the United States this procedure is almost universally spoken of as a subtotal gastrectomy. Very few surgeons, however, remove almost the entire stomach as the term implies. In the usual case the entire fundus and a portion of the body of the stomach are preserved, the amount of the latter depending upon the methods of the individual surgeon. It is more accurate, therefore, to employ the term "radical distal partial gastrectomy" for this operation.

On the other hand, it has been established by the experience of many surgeons throughout the world that in order to prevent recurrence of peptic ulceration, the gastrectomy must be extensive. All agree that the antrum and a large portion of the body of the stomach must be excised. By some it is considered important to remove as much as possible of the lesser curvature as well. If a sufficiently radical procedure is carried out, therefore, it is difficult to restore continuity by gastroduodenostomy. Furthermore, in many cases of duodenal ulcer not enough normal duodenum can be preserved distal to the level of transection to make a satisfactory anastomosis possible without danger of failure of the suture line. This has led to the almost universal adoption of gastrojejunostomy as the method of anastomosis which meets the indications best. A variety of methods has been employed and no uniformity of technique exists.

The simplest manner in which to perform a gastrojejunostomy, following distal partial gastrectomy, is to attach the entire open end of the stomach to the side of the proximal jejunal loop (Polya). The prevailing fashion, however, seems to be to employ a technique such as the Hofmeister method in which the large open end of the stomach is narrowed to a smaller diameter by partial closure before the end-to-side anastomosis is made. Many of the proponents of this technique maintain that it provides a means of diminishing the tendency to the development of the so-called "dumping syndrome." This belief comes from the original assumption that this condition is the result of unduly rapid emptying of the stomach. That this assumption is incorrect is suggested by the observation at fluoroscopic examination that all partially resected stomachs empty rapidly and also by the fact that this train of symptoms is not uncommon after proximal partial gastrectomy where of course the pylorus remains intact and there is often a tendency to delay in emptying rather than the reverse. Furthermore, the assumption that partial closure of the end of the stomach would influence the rate of emptying is erroneous because up to the point where the gastric stoma assumes the same diameter as that of the jejunum, it makes no difference how large or small it may be because the diameter of the entry point to the efferent arm of the jejunal loop is the effective diameter of the anastomosis, no matter how much of the end of the stomach remains open or closed. The essential difference, therefore, between the resected and the intact stomach is that the former lacks the pyloric sphincter which under normal circumstances controls the emptying time.

Other advocates of the Hofmeister technique maintain that it provides a way of removing a larger segment of the lesser curvature. This cannot be denied, but the necessity for this part of the technique is of theoretic importance only, provided that a large portion of stomach is excised.

The technical objections to the Hofmeister method are that it is somewhat more difficult to perform the anastomosis smoothly and that it provides a potential point of weakness where the suture line of the longitudinal closure meets the circumferential suture line at the anastomosis. It seems reasonable to believe also that the additional suturing which a partial closure of the end of the stomach entails may be in part a contributing factor in the development of early postoperative stomal obstruction.

Another technical concern is the matter of whether the jejunum should be brought up in front of the transverse colon or whether the anastomosis should be made retrocolic. There is

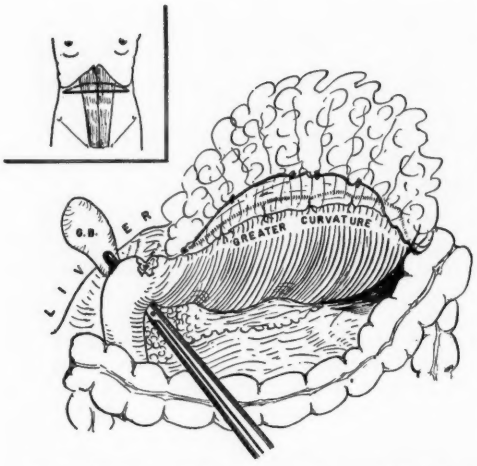

Fig. 1. Diagram showing the dissection completed ready for transection of the duodenum. The omentum has been freed from the colon for removal with the resected segment of stomach. Scissors passed behind the first portion of the duodenum to free a place for transection. Insert shows direction and length of incision, whether straight or curved upward.

some evidence that the employment of the latter method is attended by a higher incidence of stomal obstruction than when the antecolic method is used. This opinion is based upon personal experience and upon opportunities to observe the results of others who make routine use of the retrocolic anastomosis. In fact, the incidence of early stomal obstruction of sufficient severity to require a feeding jejunostomy after retrocolic Hofmeister or Polya anastomoses has been reported by Allen and Welch to be as high as 1 in 30 cases. This led Allen and Donaldson to advise the routine adoption of a double jejunostomy with one catheter directed proximally through the anastomosis to drain the stomach and another directed distally to make it possible to maintain the nutrition of the patient until the period of danger is over.

TABLE I.—COMPARISON OF RESULTS OF THREE METHODS OF ANASTOMOSIS

	Posterior Polya or Hofmeister	Anterior Polya	Gastroduodenostomy (end-to-end)
No. performed	38	99	13
Serious stomal obstruction	2	0	0
Stomal ulcer	0	1	0
Dumping	5	2	1
No. deaths	2	0	0

The possibility of stomal obstruction after a retrocolic anastomosis is enhanced when the transverse mesocolon is densely infiltrated with fat. In addition, there is always the danger of pulling away of the edge of the mesocolon from the position where it was sutured to the stomach, which may lead to obstruction of the jejunum where it passes through the mesocolon. It should be mentioned that other technical details, such as the use of a crushing clamp on the edge which is to be used for the anastomosis and the employment of the electrocautery to cut across the stomach, contribute to the development of stomal obstruction because they favor increased swelling of the tissues at the anastomosis as a result of the degree of trauma produced. These considerations obviously apply to any type of anastomosis.

So far as personal experience is concerned, Table I serves to illustrate the results obtained by the author with three methods of anastomosis following radical distal partial gastrectomy ("subtotal resection") in the treatment of duodenal ulcer. In each instance no use was made of supplementary procedures such as jejunostomy (single or double) or enteroenterostomy. Ward service cases are not included. Making allowance for the relative difference in number of cases in each group, the results obtained with the anterior Polya anastomosis as described in this communication are superior to those when the posterior anastomosis was used.

DESCRIPTION OF THE TECHNIQUE

General considerations. In the technique about to be described certain details which differ from methods in common use are worthy of comment.

In the first place, no clamps are employed because of the belief that the cut edge of the stomach which is to become a part of the anastomosis must be the subject of the least possible trauma to promote prompt healing with a minimum of swelling. Furthermore, it would be mechanically impossible to use a clamp on the stomach if the isoperistaltic anastomosis which is advocated here is employed because of the necessity of dividing the stomach transversely. This can only be done if a limited gastrectomy is carried out because of the interference of the left costal margin.

Secondly, the stomach is cut with knife and scissors rather than with a cautery, once again to avoid tissue damage for the reasons mentioned.

In the third place, the jejunal loop is usually applied to the end of the stomach in an isoperistal-

tic direction (i.e., with the proximal arm to the greater curvature and the distal arm to the lesser curvature). This method has been adopted because in the majority of patients the jejunal loop leaves the ligament of Treitz rather far to the left of the midline. The proximal loop, therefore, swings up in the isoperistaltic direction more easily and lies more naturally than if it is turned the other way, which tends to produce angulation of the proximal arm of the loop. Obstruction at the afferent end of the stoma is, of course, to be avoided because of the danger of rupture of the closed duodenal stump from increased pressure within. If the method of applying the jejunal loop to the stomach herein advocated is used, however, the stomach must be cut across in a horizontal direction or even a little higher on the greater curvature than on the lesser in order to insure that the efferent end of the stoma will be the low point from which the stomach is to empty. Thus with this technique, if the usual high level of division of the lesser curvature is adopted, a considerably larger segment of the stomach is removed than when the antiperistaltic method is employed, where the low point must be on the greater curvature (Fig. 3). The method advocated, therefore, cannot be carried out satisfactorily if a clamp is used on the stomach.

A fourth consideration is that a three layer anastomosis is advocated. As carried out, this can be done without turning the edges in any more than in the two layer method. The three layer technique makes hemostasis more certain because of the fact that the middle layer catches the majority of the vessels in the gastric wall and occludes them.

Continuous sutures are used because of the amount of time saved over the employment of the interrupted suture technique. Each layer is placed close to the preceding layer to avoid excessive turn-in and what swelling may result is kept at a minimum. With the exception of a lateral enteroenterostomy this is the only anastomosis in the alimentary canal where continuous sutures may properly be employed.

A final detail is that the omentum is freed from the colon and removed along with the resected portion of stomach. This is done because of the tendency of the omentum to interfere with the freedom of the jejunal loop as it lies in front of the colon. Furthermore, this step makes it possible to deal more easily with the gastric vessels which need be divided in this instance only at each end of the part resected, instead of having to cut and tie all the small branches of the gastroepiploic vessels along the greater curvature. Because many patients with ulcer are unusually fat as a result of frequent feeding, the omentum is likely to be thick and heavy making its presence beneath the jejunal loop still further objectionable.

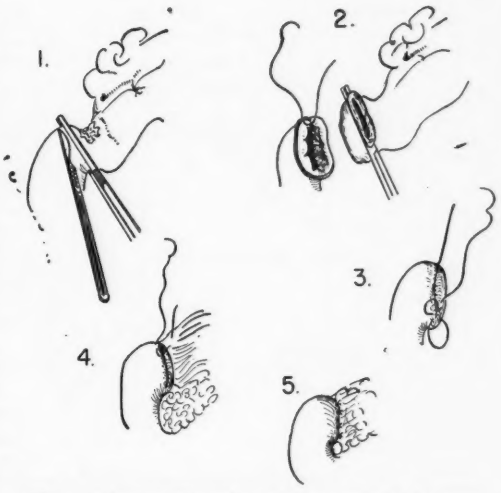

Fig. 2. Diagram illustrating various stages in the transection and closure of the duodenum. 1, Transection with a knife just distal to clamp. 2, Start of Connell suture for closure. 3, Backward continuation of this suture as a Cushing right angle stitch thus making a double layer of inversion. 4, Start of suture line between duodenal stump and tissues over the pancreas. 5, Completion of burial of duodenal stump.

ACTUAL TECHNIQUE

Incision. A transverse incision cutting both rectus muscles is made. If the costal arch tends to be angular rather than flat, the incision may be curved upward (Fig. 1, insert).

Separation of the omentum. After an exploration of the ulcer-bearing area has been carried out, the omentum is freed from the transverse colon with scissors. If one's knowledge of the embryologic development of this membrane is employed, it soon becomes obvious at what point the almost avascular plane of cleavage lies. It is always closer to the colon than one might expect. As the omentum is freed from the part where the transverse mesocolon is attached, caution must be exerted to avoid injury to some of the branches of the colic arteries and veins. The separation is carried to the left as far as the lienocolic ligament. On the right the omentum is freed all the way to the inferior border of the first portion of the duodenum (Fig. 1).

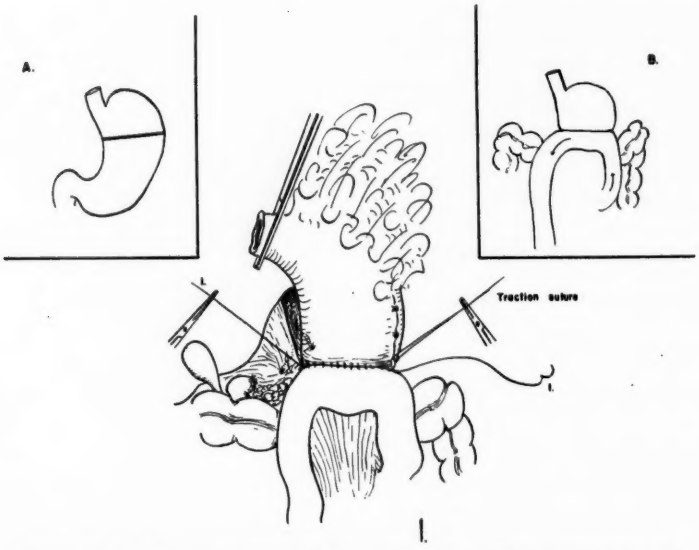

Fig. 3. Diagram illustrating start of the anastomosis. 1, First (outer) layer of the posterior aspect of the anastomosis. Insert A, Level and direction of the transection of the stomach, showing approximately the relative amount removed. Insert B, Relative positions of the proximal jejunal loop and the remainder of the stomach after completion of the anastomosis.

Mobilization and transection of the duodenum. The right gastroepiploic artery and vein are severed and tied with heavy silk. If the ulcer is not unusually adherent and if it is not located posteriorly, the posterior freeing of the first portion of the duodenum is accomplished from the pylorus distally by dividing in succession the small retroduodenal branches of the pancreaticoduodenal artery. These are to be tied usually with suture ligatures of medium weight silk. The branches which enter the duodenum along its superior surface must also be divided. In the case of an uncomplicated anterior wall ulcer, the duodenum is then ready for division and closure.

When the ulcer lies posteriorly, often with erosion of the pancreas, the technique should be modified so as to approach the ulcer-bearing portion in the opposite direction. If the attempt to free it as has been described is persisted in, it is very easy for the surgeon to lose his way, to enter the ulcer bed, and to have great difficulty in passing beyond the ulcer to a point where the normal duodenal wall is encountered. To avoid these difficulties a plane of dissection distal to the ulcer should be sought by gentle dissection with the scissors, starting along the inferior border and with no attempt at this stage to free the ulcer (Fig. 1). Injury to the common duct is avoided by staying close to the duodenal wall and avoiding the second portion in the dissection. A straight clamp (Kocher or Ochsner type) is then placed across the duodenum as close as possible to the ulcer in order to leave a maximum of free duodenum for closure, and the duodenum is cut across with a knife distal to the clamp (Fig. 2:1).

In some cases a clamp cannot be used because of the limited amount of free duodenal wall on the posterior side. In this event the duodenum is severed as close as possible to the ulcer without attempting to apply a clamp.

After it has been cut across, the distal end of the duodenum may be closed immediately, or closure may be delayed while the ulcer is being freed. Freeing of an adherent posterior wall ulcer is usually done with a knife, care being taken to clamp the vessels as they are encountered. When the ulcer has penetrated the posterior wall, the ulcer bed is left behind in the surface of the pancreas.

Closure of the duodenum. Figure 2 illustrates the steps employed (Fig. 2:2, 3, 4, 5). If a long free first portion of duodenum is available, one of the familiar methods of closure by employing a clamp may be used. In a difficult case as

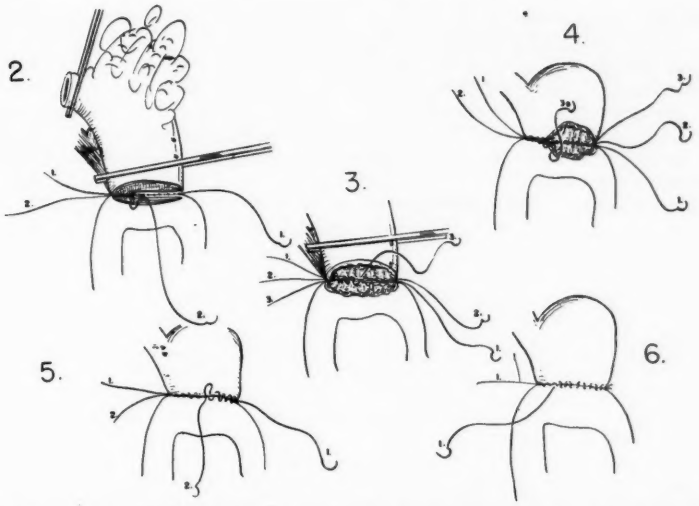

Fig. 4. Diagram illustrating various stages in the completion of the anastomosis. (Note clamp across the distal or resected portion of stomach.) 2, Start of the middle layer approximating the edges of the seromuscular coat. 3, Start of the mucosal layer (posterior). 4, Start of the anterior mucosal layer showing additional stitch (3a) to facilitate correct approximation of mucosa at lesser curvature end. (Note that these are Connell sutures.) 5, Start of anterior portion of middle layer. 6, Final layer.

described before, with only a limited length of free duodenal wall available posteriorly (pancreatic side), closure must be effected without using a clamp. In fact, the open method is preferable in all cases because of the minimum of trauma and the more exact approximation of the edges which are to heal. A Connell suture of No. 000 chromic catgut is used as a first layer. After reaching the end opposite the starting point, this suture is carried back as a Cushing right angle stitch (Fig. 2:2 and 3).

The closed end of the duodenum is then sutured against the tissues overlying the pancreas with a series of mattress sutures of silk (Fig. 2:4 and 5).

Preparation of the stomach for anastomosis. Figure 3 (insert A) shows in diagrammatic form the level and direction of transection of the stomach used when the anastomosis is made isoperistaltic, as is usually the case. A high level of division of the branches of the left gastric vessels is carried out to free the lesser curvature at the point where the stomach is to be divided. The lienocolic and gastrolienal ligaments are divided and the vessels are tied. This procedure involves severance of the left gastroepiploic artery and vein. Several of the lower vasa brevia are also divided in order to gain access to the greater curvature at a proper point for division. At this point a temporary traction suture of silk is applied (Fig. 3:1). The proximal jejunal loop is then brought up in front of the colon and fitted to the stomach. At this stage of the procedure an accurate estimate of the correct length of the proximal arm of the loop must be made. It should be short but not so short as to encroach upon the transverse colon which lies behind. In practice, a suitable length is 5 to 6 inches. Figure 3, insert B, shows diagrammatically how the loop should lie.

Performance of the anastomosis. As the anastomosis is begun it is convenient for the surgeon to move to the left side of the table. With the jejunal loop lying close to the stomach without tension, the first layer of the posterior aspect of the anastomosis is inserted, starting at the lesser curvature where an end of the suture is left for tying as the anterior aspect is completed (Fig. 3:1).

A large straight clamp is then placed across the portion of the stomach which is to be removed. This provides a handle to be held by an assistant while the remaining two posterior layers are being inserted. With a sharp knife the seromuscular coats of the jejunum and posterior stomach wall are incised to the level of the submucosa. The second or middle layer of sutures is then inserted

to approximate the seromuscular edges and at the same time catch most of the vessels in the submucosa on the gastric side (Fig. 4:2). After the completion of this layer, the mucosal incisions are made and the posterior mucosal layer is inserted, starting as with the others at the lesser curvature and passing over and over the edges to the greater curvature end (Fig. 4:3). The anterior wall of the stomach is then severed with a pair of scissors and the excised segment is removed.

The anterior aspect of the anastomosis is completed by carrying each layer back in reverse order to the starting point on the lesser curvature. As an aid to securing an accurate mucosal closure at the lesser curvature end, a fourth strand of catgut is started there and carried part way to the left as a Connell stitch. The surgeon should then move back again to the right side of the table. The original mucosal stitch is used to sew the posterior mucosal layer back to the point where this additional suture has been stopped and both are tied together. Figure 4:4 shows this additional or supplementary portion of the mucosal suture (*3a*). The anterior mucosal closure is effected with a Connell stitch placed in the mucosa only. This leaves the seromuscular edges exposed for the completion of the middle layer (Fig. 4:5). The anastomosis is finished by carrying the outer layer back to the starting point as a Cushing right angle stitch (Fig. 4:6).

It should be remembered in sewing the ends of the anastomosis that the suture layers do not come to a point but actually pass around a hemicircle corresponding to the configuration of the divided edge of the stomach at each of its curvatures. Thus in order to avoid angulation at these ends, the stitches on the gastric side should be placed somewhat closer together than those on the jejunal side to prevent twisting of the jejunum, which would favor the development of obstruction at either end of the stoma.

At the completion of the anastomosis any blood which may have accumulated in the left subphrenic area should be aspirated thoroughly to avoid the possibility of developing a subphrenic abscess if it should become infected.

Closure of the incision. The transverse incision should be closed carefully with accurate approximation of the divided rectus muscles as well as closure of the fascia of the rectus sheath. Interrupted silk sutures are used.

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2. Allen, A. W., and Welch, C. E. Jejunostomy for the relief of malfunctioning gastro-enterostomy stoma. Surgery, 1941, 9: 163–182.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE acceptance and acclaim that has been accorded Sweet's *Thoracic Surgery*[1] is expressed in the appearance now of its second edition. Laurels of this character prove not only the great interest that exists in this field of surgery, but they justify also the viewpoint of the author in presenting its subject matter.

The present volume is beautifully produced, easy to read, and the material is presented in attractive and orderly progression. This book is larger by some 30 pages than the first edition. A few of the illustrations in the first edition have been replaced by new ones designed to be more easily understood; a few new ones have been added. They have, however, preserved the same diagrammatic clarity seen in the previous volume.

Among the amplifications of the text, mention should be made of the section outlining the suture material recommended for use under various circumstances.

Due recognition is made of the advances along certain lines. Notable in this regard appears the designation of valvulotomy for pure pulmonic stenosis and valvulotomy for mitral stenosis as established procedures useful in the correction of these defects. The discussion of the operation for closure of a patent ductus arteriosus is amplified as is the procedure of esophagomyotomy. On the other hand, the author's procedure for the creation of an extracardiac shunt to relieve pulmonary congestion resulting from mitral stenosis is accorded less space. Inflammatory lesions of the esophagus and the problems inherent in their correction are again amplified.

It is comforting to know that such a source of clear, pointed, and direct technical help is available. This is particularly welcome when it is presented in succinct fashion, and given in a clear and orderly sequence. Whereas the present volume amply lives up to Dr. Sweet's hope that it would be an adequate guide for use by a well grounded surgeon beginning his thoracic surgical experience, it is equally valuable for review or as a checklist for a man of more mature experience in this field. It is a beautiful source book of established technical procedure.

HIRAM T. LANGSTON.

AMERICAN surgeons interested in the thyroid can read with profit and stimulation a new English text entitled *The Thyroid*[2] by T. Levitt. The author studied the physiology and physiologic chemistry in the laboratories of the late Professor W. A. Jolly, author of a well known text on the thyroid. Later Levitt continued his studies in this field with special work on embryology and morphologic anatomy so that he has an exceptional background for this subject.

He states that he has presented an entirely original conception of the entire problem of thyroid disease with a new classification and nomenclature. The author believes that the missing link has been supplied and that the many apparently separate entities are actually successive stages of a single disease of the toxic thyroid gland. He proposes six distinct stages which have been named according to their histologic characteristics. They are: (1) epithelial hyperplasia; (2) lymphoepithelial hyperplasia; (3) focal lymphoid hyperplasia; (4) diffuse lymphoid hyperplasia; (5) fibrolymphoid hyperplasia; and (6) fibrosis. These he considers are only milestones punctuating the uninterrupted path in the continued process of degeneration of the toxic thyroid gland.

This entirely original approach to the subject is certainly presenting this confusing problem in a new light, but one wonders if it will really clarify the problem or further complicate it. It is a far cry from the simple classifications of the American Goiter Association.

A very worthwhile contribution is a translation from the original German texts of the papers of Hashimoto and Riedel. These conditions are considered to be the last two phases of degeneration of the toxic thyroid gland.

Unusual cases of sarcoidosis and Mikulicz disease of the thyroid gland are presented. The author has seen cases of rheumatoid arthritis greatly benefited by thyroidectomy.

The basal metabolic rate, he believes, is being replaced by the radioactive iodine tests and by estimation of the protein-bound iodine. Fifty-five pages are devoted to the subject of exophthalmos and, like the entire text, this problem is beautifully illustrated. There is an interesting chapter devoted to solid edema of the legs, to the antithyroid drugs, radio-

[1] THORACIC SURGERY. By Richard H. Sweet, M.D. 2nd ed. 381 pages, 159 illustrations. $10.00. Philadelphia and London: W. B. Saunders Co., 1954.

[2] THE THYROID; A PHYSIOLOGICAL, PATHOLOGICAL, CLINICAL AND SURGICAL STUDY. By T. Levitt, M.A., F.R.C.S.(Eng.), F.R.C.S.(Ed.), F.R.C.S.I. 606 pages, 502 illustrations. $20.00. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone, Ltd., 1954.

active iodine, malignancy, the relation to the other endocrine glands, and to thyroidectomy. The author believes that the impact of radioiodine on clinical medicine is still too recent for adequate statistical assessment and that surgery still remains the ideal treatment. His personal experience is based on a study of 2,114 thyroidectomies. Gas and oxygen are routinely employed for anesthesia.

The colored illustrations, of which there are many of gross pathologic specimens, are excellent. The photographs are clear and are freely used to illustrate the text. The paper and printing are the best.

This is a book that is indeed thought-provoking with an entirely new approach to the subject of thyroid disease and one that should be read by all who are interested in the subject.

ARNOLD S. JACKSON.

THE book entitled *Ulcerative Colitis; and Its Surgical Treatment*[1] is a beautiful presentation of a most difficult surgical field. Much has been said about ulcerative colitis in the past, but rarely has so much information been gathered together and outlined in such a practical, useful fashion. The arrangement of the subject matter is extremely well titled so that as a reference work it is quickly and easily available. The section dealing with roentgenograms is outstandingly excellent. Throughout the book is a profusion of colored photographs and photomicrographs, enough to make one wonder how such a costly publication can be made available for such a reasonable price.

It is interesting to obtain Brooke's opinion concerning the possible correlation of ulcerative colitis and terminal ileitis. A short summary presents his conclusion that it is highly unlikely that Crohn's disease is just one more manifestation of ulcerative colitis.

One minor criticism might be the rather gentle emphasis on carcinoma of the colon as a complication of ulcerative colitis. A comprehensive review of important contributions to the literature is offered, but considerably more emphasis should be placed on this dread transformation. It is interesting to note that in the United States even so-called experts in this field have been lackadaisical about this feature.

A thorough discussion is given regarding technical aspects; the conscientious surgeon would do well to read this with great care. The course pursued by the author appears logical, namely, whereas ileostomy and total proctocolectomy may well be carried out as a one stage procedure, the majority of patients at present may well profit by a two stage operation. Much has been said in the United States about section of the vagus nerve for this disease; Brooke dismisses this possibility with only a brief comment.

One of the strongest parts of the book is the thorough discussion concerning ileostomy. Perhaps some American surgeons will be disappointed with the apparent lack of interest in Dragstedt's great contribution, namely, the skin-grafted ileostomy. Many surgeons have not given this advance a proper trial and have relied too heavily on new forms of cutaneous cement to apply the newer types of ileostomy bags. Opinion is divided in America at present, but some widely experienced surgeons consider that the skin-grafted ileostomy is one of the few real advances in recent years.

This book, as a whole, is exceptionally well done and is to be recommended highly.

EDWARD S. JUDD, JR.

THE book entitled *Applied Cytology*[2] by G. R. Osborn is based on the author's experience in correlating cytology and histology in over 5,000 cases during a period of 5 years. The major portion of the volume is devoted to gynecologic cytology and the general principles developed therein are modified as appropriate to exudates from other organ systems. There are 131 black and white illustrations in this monograph of 168 pages. The reproductions are excellent and impressively correlate the cytosmear with histologic preparations. One of several important features is the section in which common pitfalls to accurate cytodiagnosis are discussed and illustrated.

No exuberant claims for cytology are to be found. The approach is very practicable. Inconsequential minutiae in interpretation are eliminated and diagnoses which depend solely on histologic preparations, such as a distinction between preinvasive and invasive squamous cell carcinoma of the cervix, are frankly admitted as impossible on cytologic criteria. These and similar features fully support the author's thesis that cytology is "far from being an ultraspeciality suitable for teaching centers only . . ." Widespread acceptance and use of this book by both clinical and laboratory workers are deserved as should dispel many existing prejudices against cytodiagnosis, as well as help to eliminate much of the mysticism with which it is often viewed.

FRANK M. MAHER.

POSITIVE, essential, and practical methods for dealing with the problem of cardiac arrest are presented in the excellent 183 page handbook entitled *A Manual on Cardiac Resuscitation*.[3] The material is based upon a course in resuscitation initiated several years ago in Cleveland, under the direction of Claude S. Beck. The author writes well and covers the subject thoroughly, beginning with basic material on the history, incidence, and physiologic aspects of this extraordinary catastrophe.

Throughout the text constant emphasis is focused on two elementary components necessary for suc-

[1] ULCERATIVE COLITIS; AND ITS SURGICAL TREATMENT. By Bryan N. Brooke, M.Chir., F.R.C.S. 147 pages, 89 illustrations. $7.50. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone, Ltd., 1954.

[2] APPLIED CYTOLOGY. By G. R. Osborn, M.B., B.S. (Melbourne). 168 pages, 131 illustrations. 35s. net. London: Butterworth & Co., Ltd., 1953.

[3] A MANUAL ON CARDIAC RESUSCITATION. By Robert M. Hosler, M.D., F.A.C.S. 183 pages, 14 illustrations. $4.00. Springfield, Ill.: Charles C Thomas, 1954.

cessful resuscitation. These components are the re-establishment of the oxygen system and the restoration of the heart beat. The step by step procedures to be assumed by all personnel on the scene of the emergency are clearly defined. Brief outlines supplement some chapters, and a thorough bibliography accompanies the text.

In addition to recommending this manual to all surgeons and anesthetists, the reviewer believes that operating room nurses, house staff officers, and senior medical students would profit in the assimilation of this timely information. JOHN L. BELL.

IN his preface to *Anatomy for Surgeons*,[1] Dr. Hollinshead modestly states that he has "attempted to present in readable form that regional anatomy which is of particular importance to the surgeon . . . and to describe and interpret, with a minimal soporific effect, the anatomical facts and concepts which the surgeon has found useful." In Volume 1, which is concerned with the intricate anatomy of *the head and neck*, he has greatly exceeded this goal by producing a book filled with pertinent and detailed information which cannot fail to be interesting to the surgeons who operate in these areas.

The various chapters are concerned with the cranium and its contents, the orbit, the ear, the nose and paranasal sinuses, the fascia and fascial spaces of the head and neck, the face, the jaws, palate and tongue, the pharynx and larynx, and the neck. Structures, relationships, and common variations of importance to the clinician are described and illustrated in considerably more detail than they appear in most general textbooks or atlases. Included are references to original sources, and much information previously inaccessible to the active surgeon.

"The illustrations are purely diagrammatic, and are planned to accompany the text in much the same manner that one draws diagrams upon the blackboard to illustrate points in a lecture." It is assumed that the reader is familiar with the plates in the standard atlases, and these simple line drawings illustrate additional important details and relationships with great clarity.

Suggestions as to specific surgical procedures are interspersed throughout the text, possibly to add some interest for medical students or house officers in surgical training. These have been reviewed by clinicians associated with the author on the staff of the Mayo Clinic. As noted by the author, some of these procedures undoubtedly will not stand the test of time, but the basic anatomy will remain the same.

Wisely, the work is not limited to the anatomic knowledge necessary to today's surgery. Dr. Hollinshead notes that "details and concepts of anatomy which were of no interest to the surgeon even ten years ago have become, through advances in technic, essential information."

Anatomy is basic to all surgery, and this work contains a wealth of interesting and helpful anatomic details and concepts concerning the head and neck areas. It should be valuable to, and appreciated by, surgeons operating in these fields.

FRANK MCDOWELL.

EVERY surgeon who had the privilege of seeing active service in World War I or II will live again in retrospect through some of the stirring days and weeks of those war years as he reads the volume on *Surgery*, a part of the *Medical History of the Second World War*.[2] He will recall some of the victories won when the odds were against him, and probably still more vividly some of the tragic defeats when multiple injuries, secondary hemorrhage, shock from blood loss and penetrating cold combined to snatch away a life that a chain of brave and tireless workers—stretcher bearers, ambulance drivers, orderlies, nurses—had done their best to save.

This volume of 25 chapters by a group of distinguished contributors covers the entire field of war surgery. The chapter headings,—"Treatment of Wounds," "Transfusion of Blood and other Fluids," "Shock and Resuscitation," "Anaesthesia," "Burns," continuing through all the fields of regional surgery, and concluding with "Blast," "Crush Syndrome," "Immersion Foot," "Amputations and Artificial Limbs," "Physiotherapy and Rehabilitation," "Non Pulmonary Tuberculosis," and two final chapters on "Traumatic Effects of the Atomic Bomb" and "Prisoner-of-War Camp Surgery" indicate the scope of this extensive survey, and how completely the task has been accomplished.

With so wide a horizon before him and with so many points of interest it is difficult to select specific subjects and chapters for especial mention. The contributions of Sir Gordon Gordon-Taylor,—part 3 of Chapter 1 on the "Treatment of Wounds," outlining the changing conditions that confronted the medical corps in a war of rapid movement and which led to the development of the mobile field surgical unit as an important factor in the improved and early surgical care of the wounded; and the 130 page chapter (chapter 4) on "Abdominal and Thoraco-Abdominal Injuries" are classic examples of the facility of expression, the completeness, and the experienced judgment that one has come to expect in the papers of the dean of British surgeons. This chapter (4) includes not only a review of the experiences of surgeons from every theatre of the war from Africa to Malaya, Italy, and France, but of injuries sustained in air raids on the home front also, and includes 600 cases which formed the basis of Gordon-Taylor's Bradshaw lecture in 1942.

The chapters on "Orthopedic Surgery" (H. Osmond-Clarke, J. Crawford Adams, Sir Thos. Fairbank, J. C. Scott), on "Burns" (Sir Zachary Cope,

[1] ANATOMY FOR SURGEONS: THE HEAD AND NECK. By W. Henry Hollinshead, Ph.D. Vol. I. 560 pages, 326 illustrations. $10.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1954.

[2] MEDICAL HISTORY OF THE SECOND WORLD WAR: SURGERY. Edited by Sir Zachary Cope, B.A., M.D., M.S., F.R.C.S. 772 pages, illustrated. £4. London: Her Majesty's Stationery Office, 1953.

G. H. Morley), on "Plastic Surgery" by a group of 14 contributors, on "Maxillo-Facial Injuries" (Sir W. Velsey Fry), and on "Neurosurgery" (Sir Zachary Cope, Sir Hugh Cairns, Sir Geoffrey Jefferson, L. Guttmann) arouse mixed feelings. One is constantly moved to admiration by the excellent results obtained under trying circumstances; sympathy for the lack of understanding and co-operation on the part of administrative "higher ups" with resulting frustration and waste of personnel, evidenced for example in Battle's "War History of Plastic Surgery in the Army"; regret that the obvious necessity for close co-operation between groups of specialists, for example the "Trinity" of maxillofacial, neurosurgical, and ophthalmic units, was at times so difficult to achieve.

One might comment on how difficult it is for a military organization to abandon long accepted practices even after their grave disadvantages have been widely recognized, for example the use of coagulating methods in the treatment of burns. Again one is struck by the tendency of the military mind to accept "gadget-like" methods of treatment, even though they run contrary to simple and basic surgical principles; for example, the constant irrigation treatment of burns of the extremities that actually favored water logging and maceration of the injured areas, and the repeated spraying of burned surfaces with melted wax with complete disregard of the primary importance of protection of open wounds from infection.

In reading this volume one is constantly impressed with the fact that three factors were of major importance in the surgical successes and advances of World War II: the availability and generous use of whole blood; the constantly accelerated evacuation of the seriously wounded, and particularly the early evacuation by air of patients with multiple and serious injuries; and, during the later years, the availability in adequate amounts of the sulfonamides and, still more, of penicillin. In emphasizing these factors one does not minimize the devotion and skill of all ranks that had a share in the care of the sick and wounded. That same devotion and skill, however, have characterized men and women in similar tasks from the time of Ambroise Paré and Florence Nightingale. It was the good fortune of the wounded soldier in World War II to have fought in an era when medical science had advanced to the plane it has reached today; it was his misfortune that the science of human relations had failed so completely to keep pace with the advances that have been made in many other fields of human endeavor.

SUMNER L. KOCH.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

NOVENO CONGRESO INTERAMERICANO Y VIGESIMOSEPTIMO CHILENO DE CIRUGIA. Presidente: Dr. Leonidas Aguirre Mac-Kay. Fasciculo II: Co-relatos y contribuciones. Published under the direction of Dr. Emilio Villarroel Gonzalez. 330 pages, illustrated. Santiago: Sociedad de Cirujanos de Chile, 1954.

DIE BESTIMMUNG DER FRUCHTBAREN UND UNFRUCHTBAREN TAGE DER FRAU MIT HILFE DER KOERPERTEMPERATUR. By Dr. Med. Gerd K. Doring. With a foreword by Prof. Dr. W. Bickenbach. 20 pages, 3 illustrations. DM 1.90. Stuttgart: Georg Thieme Verlag, 1954.

ROENTGEN-DIAGNOSTICS. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. 1st American ed. (Based on the 5th German ed.). English translation arranged and edited by James T. Case, M.D., D.M.R.E. (Camb.). Vol. 4. Gastrointestinal Tract. Gynecology, Urology. 930 pages, 1007 illustrations. $50.00. New York: Grune & Stratton, 1954.

CLINICAL ROENTGENOLOGY. Vol. 2. The Head, Neck and Spinal Column. By Alfred A. de Lorimier, M.D., Henry G. Moehring, M.D., and John R. Hannan, M.D. 464 pages, illustrated. $18.50. Springfield, Ill.: Charles C Thomas, 1954.

THE FEMALE SEX HORMONES. By Leon J. DeMerre, Ph.D. 219 pages. $3.50. New York: Vantage Press, Inc., 1954.

THE DIGITAL CIRCULATION. By Milton Mendlowitz, M.D., F.A.C.P. 182 pages, 60 illustrations. $6.75. New York: Grune & Stratton, 1954.

TEXTBOOK OF PEDIATRICS. Edited by Waldo E. Nelson, M.D. With the collaboration of 70 contributors. 6th ed. 1581 pages, 438 illustrations. $15.00. Philadelphia, London: W. B. Saunders Co., 1954.

UROLOGIE; OPERATIVE THERAPIE-KLINIK-INDIKATION. By Dr. H. Boeminghaus. 1044 pages, 599 illustrations. DM 110. München-Gräfelfing: Werk-Verlag Dr. Edmund Banaschewski, 1954.

POSTCIBAL SYMPTOMS AFTER PARTIAL GASTRECTOMY FOR PEPTIC ULCER. By Sten Meurling. 127 pages, illustrated. From the Surgical Clinic, Royal Academic Hospital, University of Uppsala, Sweden and the Surgical Clinic, Karlskoga Hospital, Sweden. Also published as supplement 3 to Acta Societatis Medicorum Upsaliensis, 1953.

TEXTBOOK OF OPERATIVE GYNAECOLOGY. By Wilfred Shaw, M.A.(Camb.), M.D., F.R.C.S.(Eng.), F.R.C.O.G. 443 pages, 382 illustrations. $19.00. Edinburgh and London: E. & S. Livingstone, Ltd., 1954.

PREFRONTAL LEUCOTOMY AND RELATED OPERATIONS; ANATOMICAL ASPECTS OF SUCCESS AND FAILURE. By Alfred Meyer, M.D.(Bonn), and Elizabeth Beck. 60 pages, 20 illustrations. 10/6 net. Published for the William Ramsay Henderson Trust. Edinburgh and London: Oliver & Boyd, 1954.

NECK DISSECTIONS. By James Barret Brown, M.D., and Frank McDowell, M.D. 163 pages, 82 illustrations. $7.50. Springfield, Ill.: Charles C Thomas, 1954.

AN OUTLINE OF PRESENT DAY THORACIC SURGERY. By Robert I. Carlson, M.D. 158 pages. St. Louis: Educational Publishers, Inc., 1954.

CLINICAL MEASUREMENT OF UTERINE FORCES IN PREGNANCY AND LABOR. By S. R. M. Reynolds, Ph.D., D.Sc., Jerome S. Harris, M.D., and Irwin H. Kaiser, M.D., Ph.D. 328 pages, 99 illustrations. $9.50. Springfield, Ill.: Charles C Thomas, 1954.